ANNALS OF
INTERNAL MEDICINE

VOLUME 12 SEPTEMBER, 1938 NUMBER 3

THE HEART IN PULMONARY TUBERCULOSIS; ELECTROCARDIOGRAPHIC CONSIDERATION *

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THIS report and discussion is based on impressions gained from clinical observation, including a roentgenological and electrocardiographic study, of 416 cases of active tuberculosis and of 44 inactive cases. This series is believed to represent the largest group studied to date. It is unique because the average age of the patients is somewhat higher than is usually found in a sanatorium group. Approximately 25 per cent of the active cases have been observed over a period of two to seven years. During this period of observation, repeated cardiograms and roentgen-rays were made. Circulatory disturbances dominate the clinical symptoms and are the primary cause of death in many instances. Thirty-eight of the active cases showed an arterial hypertension; in 19 of these the hypertension was classed as minimal, in 8 cases moderate, and in 11 cases severe. General arteriosclerosis was noted in 14 of the hypertensive group. Renal lesions of significance were proved in only one instance.

The average age of the 378 cases with normal or subnormal arterial tension was 38.5 years; that of the hypertension group 42 years. Of the hypertension cases 42.1 per cent were in the third decade; 47.4 per cent in the fourth decade; 5.3 per cent in the fifth decade, and 5.2 per cent in the sixth decade of life. The youngest case was 30 years, the oldest 60. A survey of 109 cases of hypertensive heart disease not associated with active tuberculosis diagnosed at this facility showed 22 per cent in the third decade, 37.6 per cent in the fourth decade, 21.1 per cent in the fifth decade, 19.2 per cent in the sixth decade. Matz [14] in a report of study of 330 veterans with heart disease found 59 cases of arteriosclerosis with an average age of 42.7 years and 17 with essential hypertension, average age 35.6 years. White [15]

* Received for publication June 28, 1937.
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Study was made at Veterans Administration, Tucson, Arizona.

in a series of 709 cases of hypertensive heart disease found 62 per cent in the sixth and seventh decades while only 21 per cent were under 50 years of age. The pulmonary tuberculosis cases with hypertension show a higher percentage in the third and fourth decades than is indicated in the reports of the non-tuberculous cases. The incidence of arterial hypertension in the cases reported at this time is approximately 8 per cent. Complete cardiovascular examination has been limited to those cases presenting either subjective or objective findings suggesting impairment of cardiac function. The incidence of hypertension in the total number of tuberculous patients treated at this facility has not been determined but probably does not exceed 1 per cent.

Mediastinal distortion resulting in sudden or slow shifting of the heart and great vessels is not an uncommon occurrence in pulmonary tuberculosis. A slowly developed distortion is the result of (1) a unilateral narrowing of the lung field due to slow contraction of extensive fibrotic processes within the lung; (2) contraction of the lung, a sequela of a compressed lung by artificial pneumothorax, the lung becoming cirrhotic and atelectatic as a result, and (3) artificial pneumothorax or hydrothorax of the opposite side. Sudden development of distortion, associated with shifting of heart, is usually due to atelectasis, the result of blocking of a bronchus causing partial or complete collapse of lung, or to pressure from the opposite side as the result of spontaneous pneumothorax.

The shifting of the anatomical position of the heart is a possible cause of the abnormalities of the QRS group of the electrocardiogram; a shift to the left is expected to cause a right axis deviation unless there is a rotation on the anatomical axis sufficient to neutralize the effect of the lateral displacement. A similar though less marked change occurs when the heart is displaced to the right with a tendency to left axis deviation. Experimental work by Meek and Wilson [1] on the dog's heart demonstrated that rotation of the displaced heart on its longitudinal axis materially affected the electrical axis. Elevation of the diaphragm, especially the left, causes a rotation of the heart, thus affecting the electrical axis oppositely from what is expected in many instances. The correlation of electrocardiographic changes in the cases under discussion is given in table 1, A and B. In the 108 cases showing shift of the heart to the left, 26.8 per cent showed right axis deviation, 9.2 per cent left, and 64 per cent none at all. In the 44 cases showing shift of heart to the right, 11.4 per cent showed left axis deviation, 13.6 per cent right, and 75 per cent none at all. In the 226 cases showing no shift 5.8 per cent showed left axis deviation, 12.4 per cent right, and 81.8 per cent none at all. The above group included all cases of active pulmonary tuberculosis, showing normal or subnormal arterial tension. In the group showing arterial hypertension listed in table 1–B, there are three cases recorded as shift of heart to the right, none of which showed axis deviation; 11 cases showed shift to the left, of which 27.2 per cent had

TABLE 1A

Active Pulmonary T.B. (Normal or Subnormal Arterial Tension)

X-Ray	Electrocardiographic Changes																									
			Elec. Axis			P-Wave			Q-Wave			Q-R-S				S-T		T-Wave				Percentage of Total					
Position of Heart	Number of Cases	Normal Ekg.	R-Axis Deviation	L-Axis Deviation	No Axis Deviation	Low Voltage	Increased Amplitude	Increased Duration	Q_1	Q_2 and $_3$	Q_3	I–V Block	Slurring R or S	Low Voltage	R and S Leads 1–2–3	Elevation	Depression	Low Voltage	Increased Volt. —No ST	Inverted I and II	Inverted II and III	Disturbance Rhythm	P-Wave Abnormal	QRS Abnormal	ST Abnormal	T-Wave Abnormal	Q-Wave Abnormal
Shift of heart to R.....	44	5	6	5	33	8	2	3	1	0	2	2	9	5	0	2	2	6	5	0	2	11.3	34	36.3	9	29.5	6.8
Shift of heart to L.....	108	13	29	10	69	23	6	9	3	1	5	7	25	8	7	7	3	19	6	0	5	8.3	38.8	43.5	9.2	27.7	8.3
No shift of heart.....	226	64	28	13	185	31	14	22	1	1	3	17	22	11	19	13	9	38	11	3	8	10.6	31.4	30.5	9.7	26.5	2.2

TABLE IB

Active Pulmonary T.B. (Arterial Hypertension)

X-Ray	Electrocardiographic Changes																								
			Elec. Axis			P-Wave			Q-Wave			Q-R-S				S-T		T-Wave				Percentage of Total					
Position of Heart	Number of Cases	Normal Ekg.	R-Axis Deviation	L-Axis Deviation	No Axis Deviation	Low Voltage	Increased Amplitude	Increased Duration	Q_1	Q_2 and $_3$	Q_3	I–V Block	Slurring R or S	Low Voltage	R and S Leads 1–2–3	Elevation	Depression	Low Voltage	Increased Volt. —No ST.	Inverted I and II	Inverted II and III	Disturbance Rhythm	P-Wave Abnormal	QRS Abnormal	ST Abnormal	T-Wave Abnormal	Q-Wave Abnormal
Shift of heart to R....	3	0	0	0	3	0	1	0	0	0	0	0	1	0	0	0	2	1	0	1	0	0	33.3	33.3	66.6	66.6	0
Shift of heart to L.....	11	1	3	4	4	2	1	0	0	0	0	2	2	0	1	0	2	1	0	1	1	0	27.2	45.4	18	27.2	9
No shift of heart.....	24	2	2	8	14	2	5	2	0	0	2	2	5	1	0	0	3	5	0	1	2	8.1	37.5	33.3	12.5	37.5	8.1

right axis deviation, 36.4 per cent left, and 36.4 per cent none at all. In the 24 cases showing no shift of the heart, 8.3 per cent showed right axis deviation, 33.3 per cent left, and 58.4 per cent none at all. The criteria as outlined by Pardee [4] were employed in determining the electrical axis. When the term "axis deviation" is used in this discussion we refer to the electrical axis. When the term "shift" or "shifting of the heart" is used we refer to the anatomical axis.

Brumfiel [2] made a study of the degree of circulatory embarrassment in cases showing distortion of the mediastinum combined with cardiac displacement. He concluded that there was more pronounced functional impairment in cases of this type than in those showing no displacement.

The writer's observation of cases showing distortion of the mediastinum of a moderate or marked degree, tends to confirm the findings of Brumfiel: Dyspnea, out of proportion to the degree of pulmonary involvement; simple tachycardia, frequently complicated by paroxysmal attacks; a higher percentage of cases presenting the more pronounced evidences of right heart dilatation as manifested by edema of the extremities, hepatic engorgement, and digestive disturbances. Abnormalities of the QRS and T-waves of the electrocardiograms are also more common as will be noted by referring to tables 1–A and 1–B.

A diagnosis of mediastinal distortion, associated with shifting of the heart to the right or left, was made by roentgenological examination in 166 cases or 39.9 per cent of the total number of active cases studied. There was a shift of the heart to the left in 119 instances. Of these 111 were due to contraction of the left lung field and 8 to pneumothorax or hydropneumothorax on the right. A shift to the right was found in 47 cases, 39 due to narrowing of the right lung field and 8 to pneumothorax or hydropneumothorax on the left.

Synopses of Case Histories

The cases reported have been selected as representing some of the interesting electrocardiographic changes noted in the series.

Case Reports

Case 1. Male, white, aged 37. The history indicates onset of pulmonary tuberculosis in 1918. Negative for luetic infection. No history of anginal syndrome. Figure 1 (top) represents a roentgenogram made December 1931 indicating a far advanced pulmonary tuberculous involvement, moderate contraction of the left lung field with slight shifting of heart and mediastinum to the left. There is also a suggestion of pleuropericardial adhesions in the upper mediastinal area. Blood pressure: systolic 84, diastolic 58. Figure 1 (bottom), the electrocardiogram of this patient, presents a Q_1 and a slight prolongation of the PR interval.

Case 2. Male, white, aged 35. The history indicates the onset of pulmonary tuberculosis in 1923; there were pulmonary hemorrhages at about this time. There was no history of luetic infection, and the serologic tests were negative. Figure 2

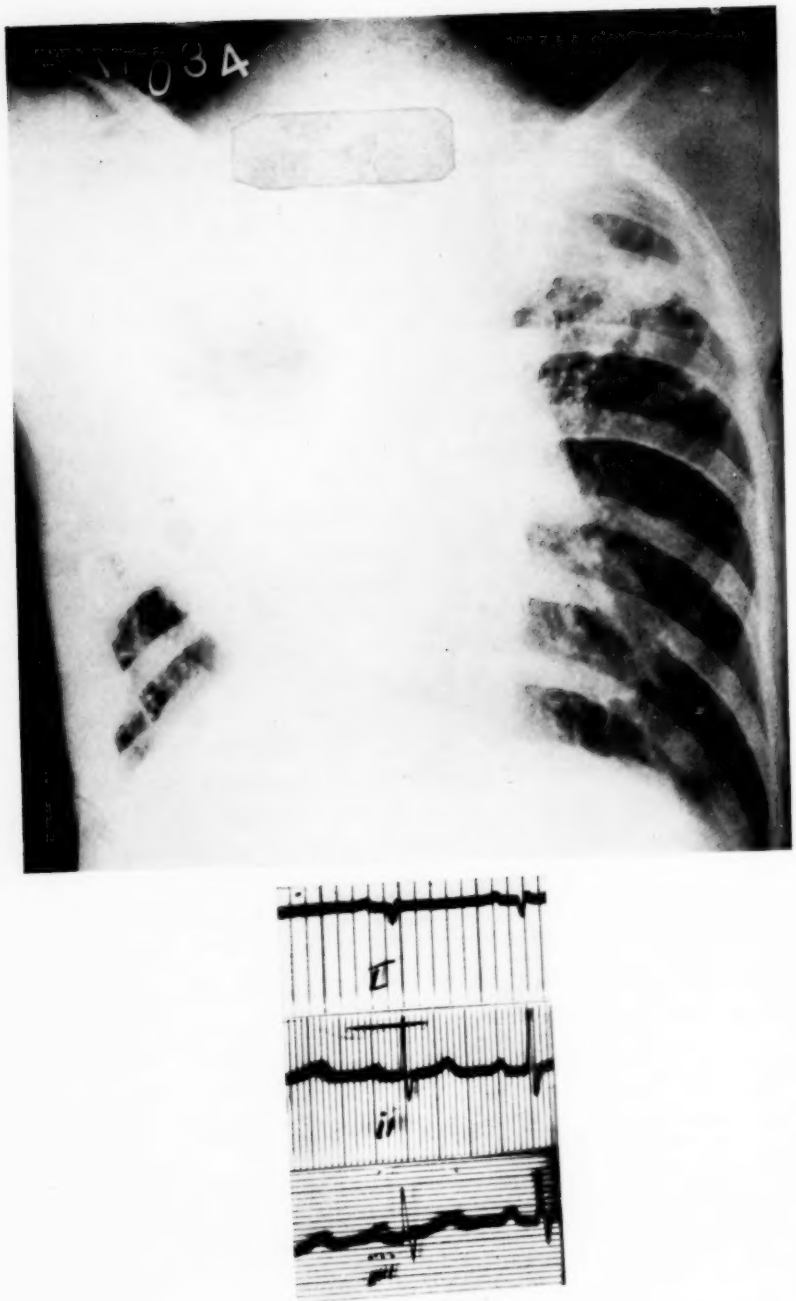
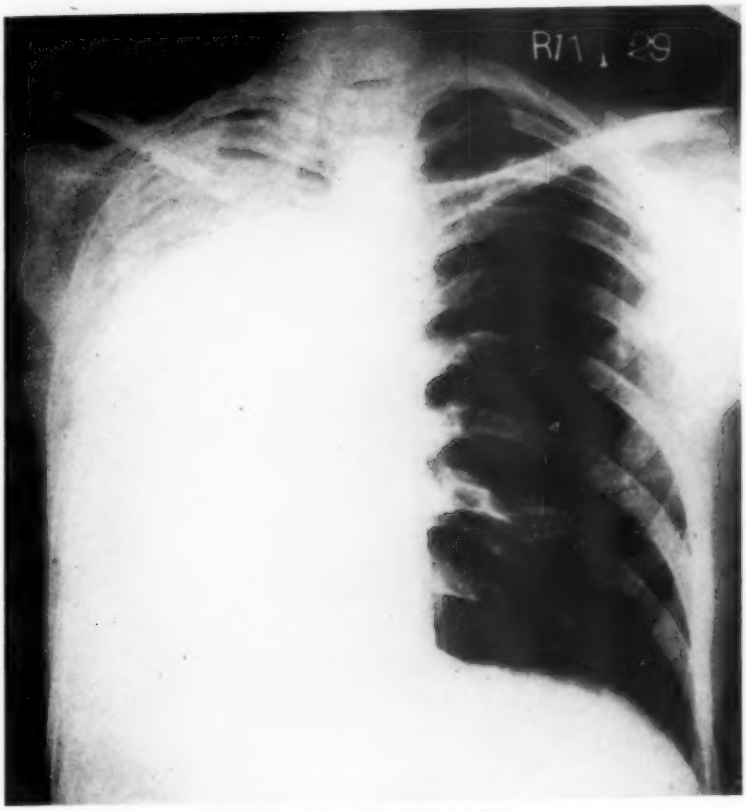


FIG. 1. Case 1.



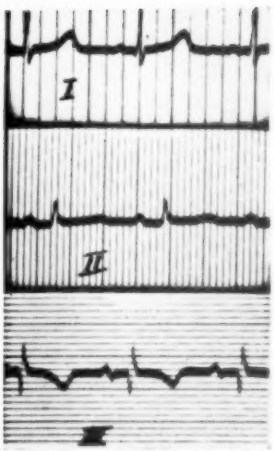


FIG. 2. Case 2.

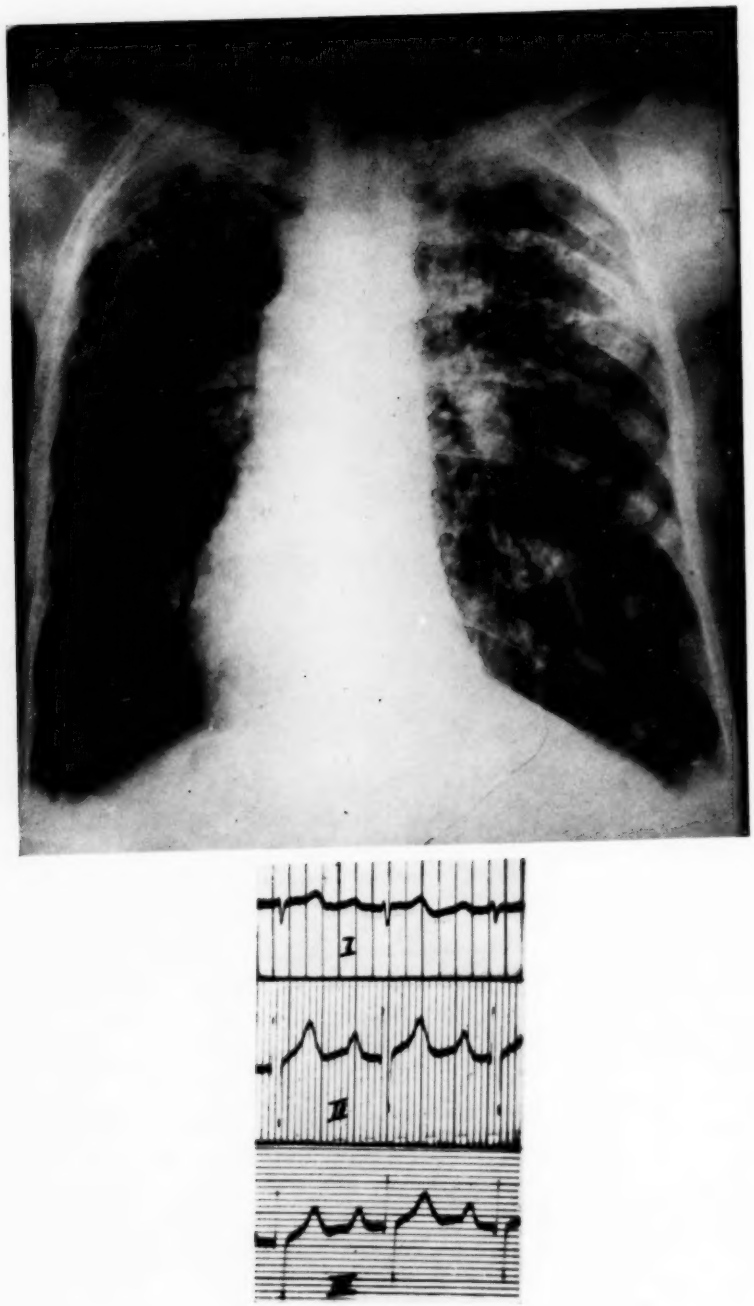
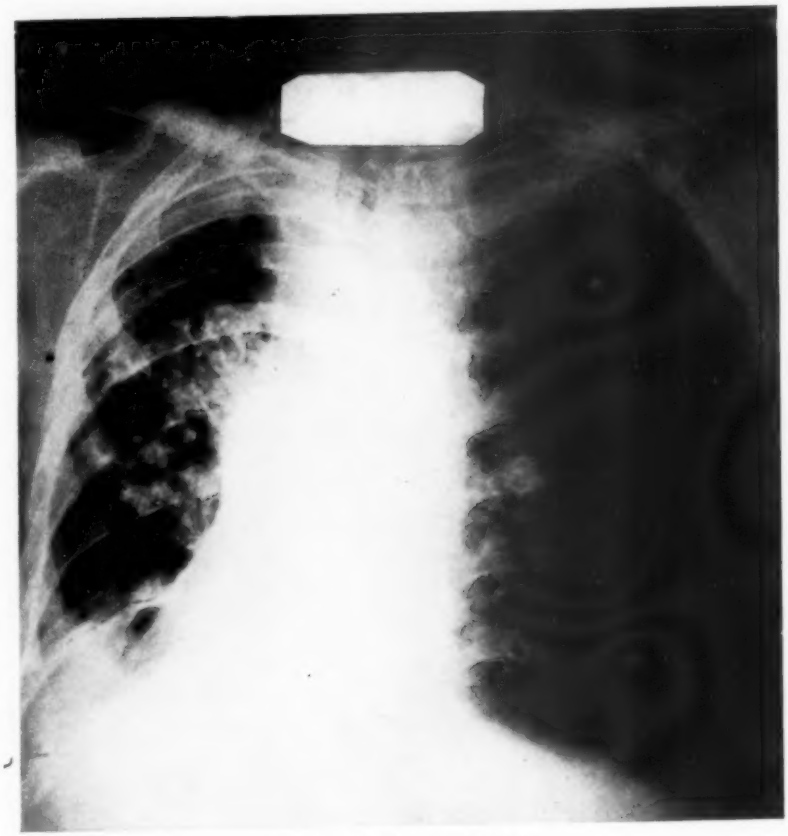


FIG. 3. Case 3.



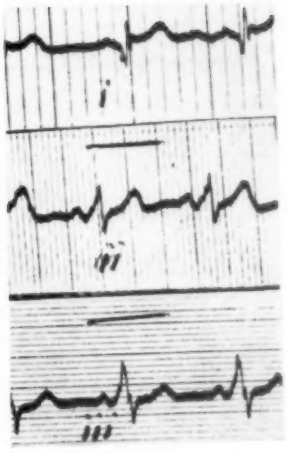
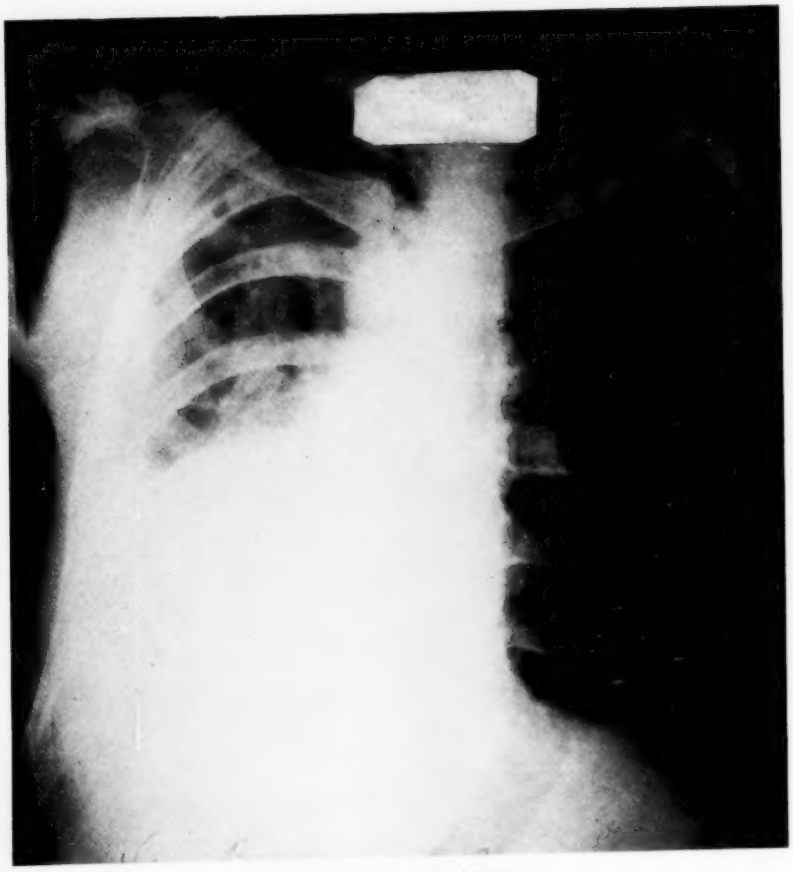


FIG. 4. Case 4.



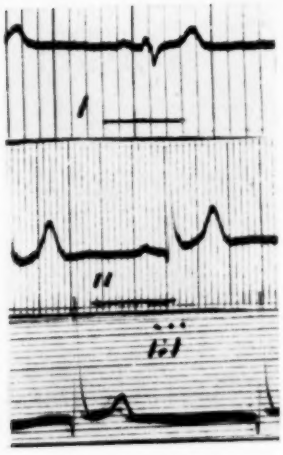
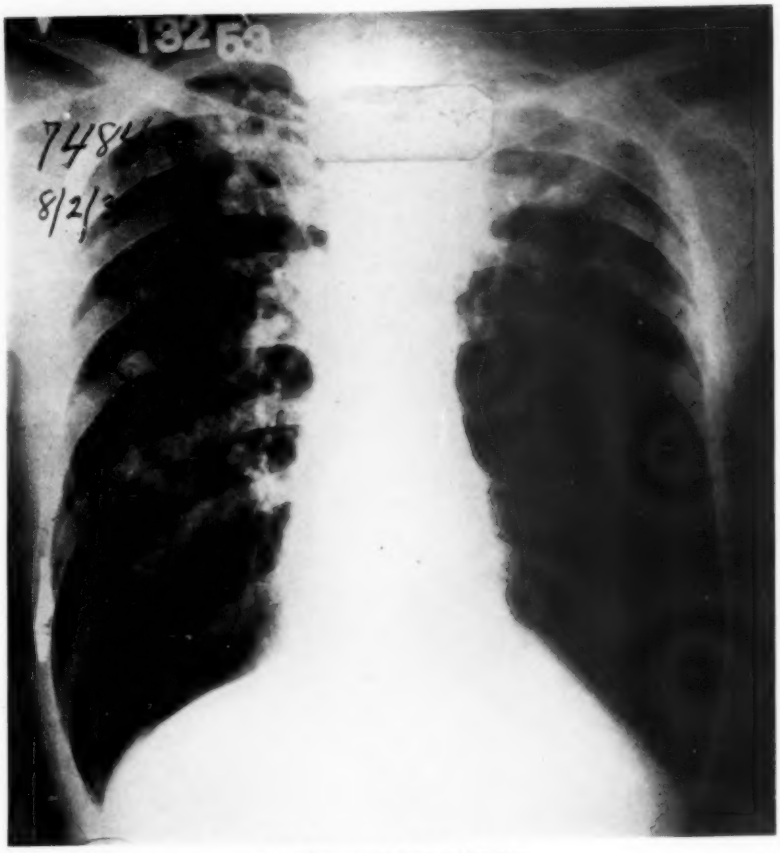


FIG. 5. Case 5.



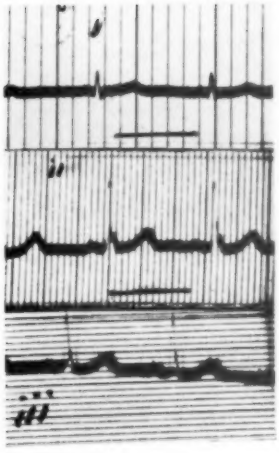
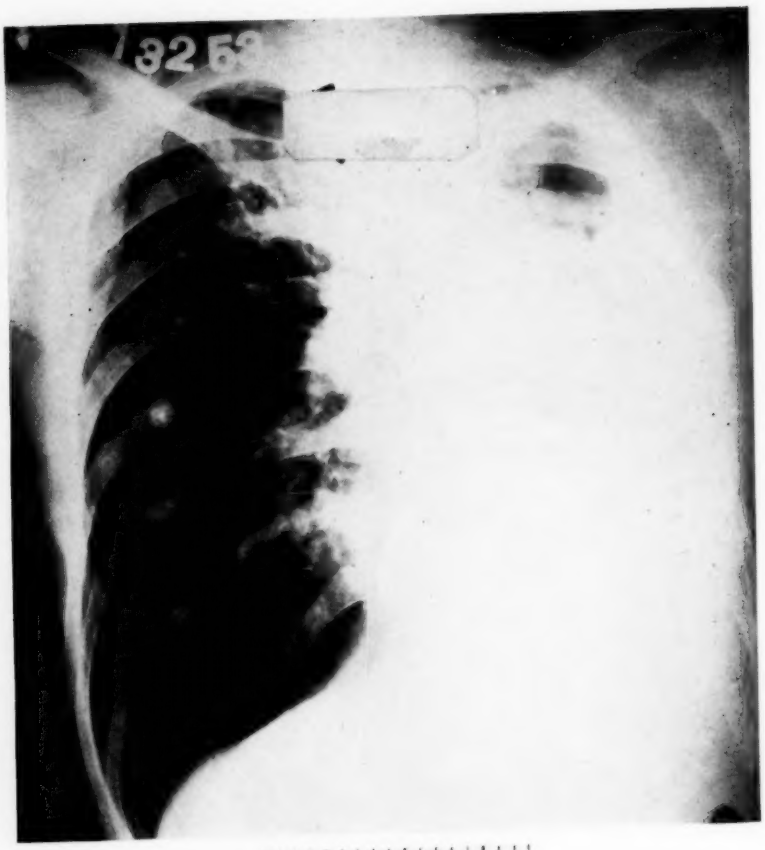


Fig. 6. Case 6.



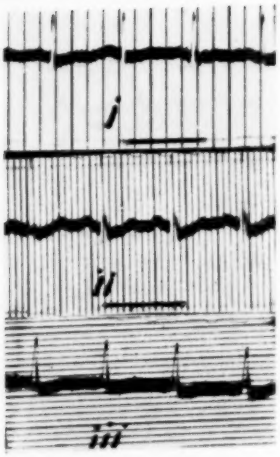
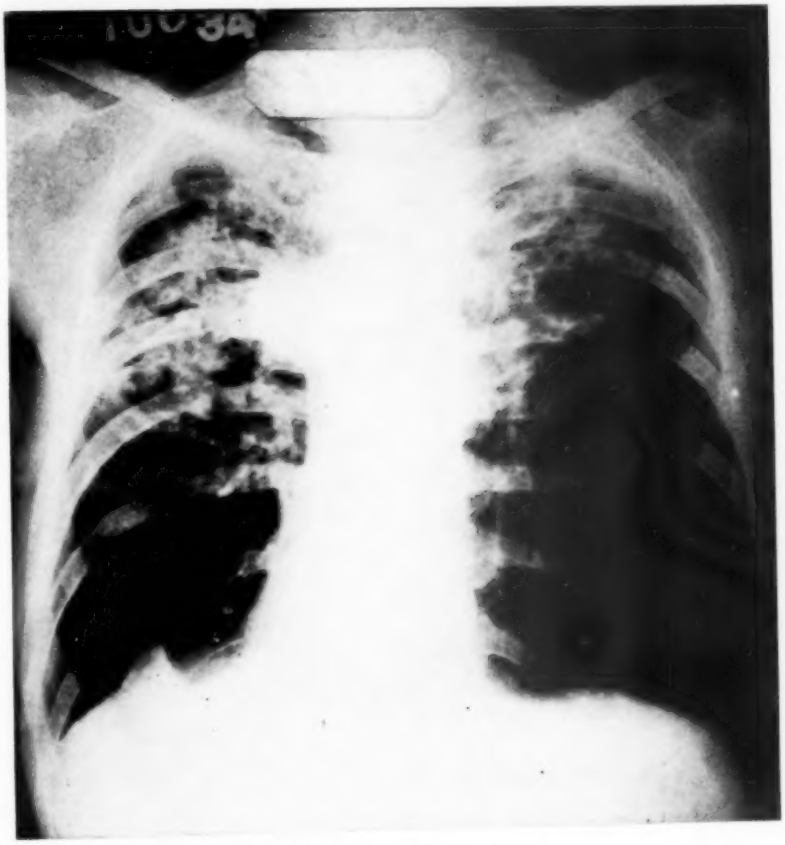


Fig. 7. Case 6.



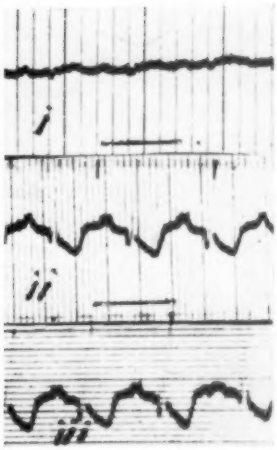


Fig. 8. Case 7.

(top) represents a roentgenogram made November 1929 indicating extensive tuberculous involvement of the left lung with marked narrowing of the lung field due to massive collapse and marked shifting of heart and mediastinum to the left. Blood pressure: systolic 100, diastolic 70. Figure 2 (bottom) represents an electrocardiogram made September 1930 showing a Q_3 with inverted T_3.

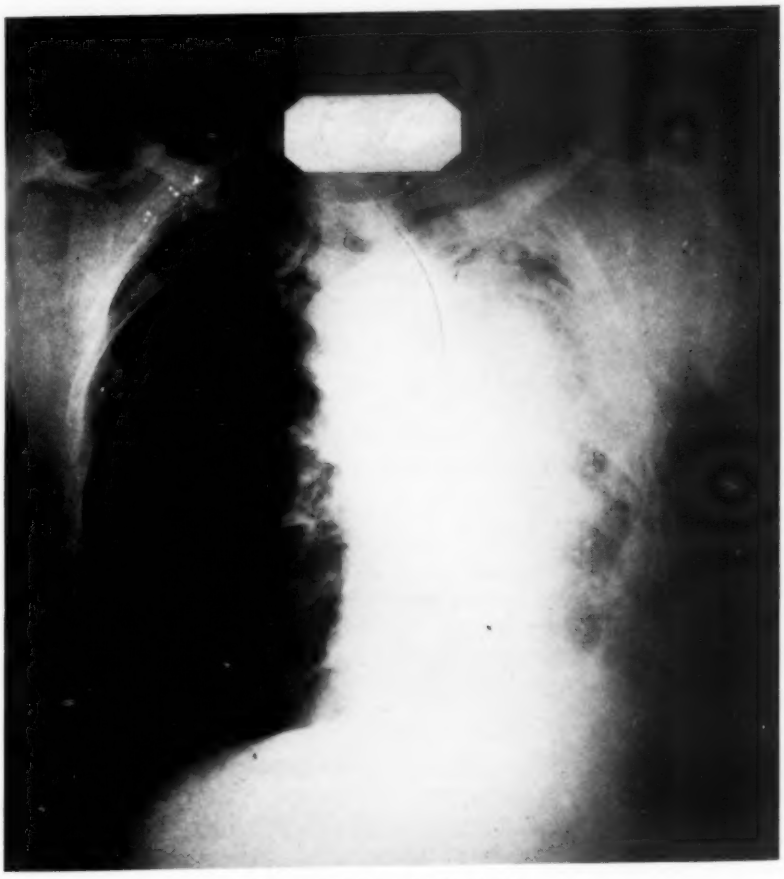
Case 3. Male, white, aged 36. The history places the onset of pulmonary tuberculosis in 1923. No history of luetic infection; blood Wassermann negative. No anginal syndrome. Figure 3 (top) represents roentgenogram made May 1930 indicating an extensive bilateral, active tuberculosis. The heart is in median position but there are indications of pleuropericardial adhesions in the upper mediastinal area. Figure 3 (bottom) shows an electrocardiogram made May 1930. Attention is invited to the high amplitude of P_2 and P_3, the equal amplitude of R and S in Leads II and III with a rather unusual type of ST and a high amplitude of T_2 and T_3.

Case 4. Male, white, aged 34. A diagnosis of pulmonary tuberculosis was made in 1918. Phrenic nerve exeresis, permanent, was performed on the left side in 1930. No cardiac pain, but complains of "rapid heart action." Blood pressure: systolic 114, diastolic 86. Figure 4 (top) represents roentgenogram made January 1930 which shows far advanced, active lesion, left; fibrotic right; distortion of the mediastinum with shifting of heart to the left, elevation of left diaphragm, and general narrowing of the lung field. Figure 4 (bottom) represents an electrocardiogram made March 1930 which shows a Q_1, slurring of R, elevation of RST_1, and intraventricular block. This patient left the hospital in 1930 and died March 16, 1932 in another institution. No congestive failure or symptoms indicating increased impairment of cardiac function were noted. Postmortem findings were as follows:

1. Peritonitis, acute, general, due to acute suppurative appendicitis, with rupture.
2. Appendectomy, recent.
3. Tuberculosis, pulmonary, chronic, apex right and both lobes left.
4. Pleurisy, tuberculous, chronic, fibrous, adhesive, over all lobes, bilateral; right slight, left marked.
5. Diaphragmatic and pericardial adhesions, bilateral; right slight, left marked.
6. Dilatation, cardiac, concentric.
7. No demonstrable coronary disease.

Case 5. Male, white, aged 36, diagnosed pulmonary tuberculosis in 1928. "Pleurisy pain" left lower chest. Paracentesis left chest in 1928, presumably for pleural effusion. Blood pressure: systolic 110, diastolic 70. Figure 5 (top) represents a roentgenogram which shows narrowing of the left lung field, thickened pleura left lower, apparent elevation of the left diaphragm, and cavitation in right upper. Figure 5 (bottom), the electrocardiogram made February 1930, shows low voltage of P, increased duration of QRS interval (intraventricular block), slurring of R_1 and elevation of RST_2 and $_3$.

Case 6. Male, white, aged 43. The diagnosis of pulmonary tuberculosis was made in 1928. There was a history of chancre about 1910. No collapse-therapy. Blood pressure: systolic 106, diastolic 70. There are no physical findings suggestive of a cardiovascular syphilis. Figure 6 (top) represents a roentgenogram made August 2, 1935, which shows a bilateral, active tuberculous lesion, with cavitation in the right upper; heart in the median position, of the small asthenic type. Figure 6 (bottom) reproduces an electrocardiogram made August 10, 1935, which shows no abnormality of importance. On November 15, the patient complained of sudden onset of dyspnea and weakness. Figure 7 (top) represents a roentgenogram made November 15, 1935, which shows opacity of the right lung, and the mediastinum distorted with shifting of the heart to the right. Diagnosis: Acute atelectasis right lung, due to sudden blocking of the bronchus. Figure 7 (bottom) reproduces a



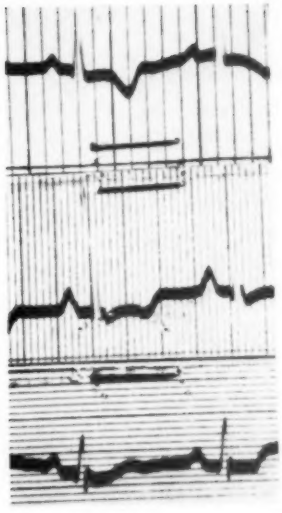


FIG. 9. Case 8.

cardiogram made on the same day. Note the change in voltage of T and the depression of RST_2 and $_3$. This cardiogram is not unlike the EKG with staircase ST recorded by McGinn and White,[13] associated with acute *cor pulmonale*. This case terminated in death some two months later. No post mortem was permitted.

Case 7. Male, white, aged 51. The onset of tuberculosis was in 1928. The history is negative for anginal syndrome. No arteriosclerosis is demonstrable. The systolic blood pressure was 118 and the diastolic 80. Figure 8 (top) represents a roentgenogram made September 1932, which shows bilateral, active tuberculosis with extensive cavitation; the heart of the asthenic type, and in median position. There is a suggestion of adhesions around the base of the heart. Figure 8 (bottom) reproduces an electrocardiogram made September 1932. There is pronounced disturbance in RST_2 and $_3$, with inverted T_2 and $_3$. (No digitalis.) The present status of this patient is unknown.

Case 8. Male, white, aged 44. The onset of pulmonary tuberculosis was in 1918. Pneumothorax was induced on the right in 1922 and continued until about 1930. There is no record of blood pressure prior to December 1932, date of first cardiovascular examination. The systolic blood pressure was then 226 and the diastolic 150. Figure 9 (top) represents a roentgenogram made December 1935. It shows no change of importance from that taken in 1932. There is marked contraction of the right lung field with distortion of the mediastinum and shifting of heart to the right. The distortion is presumably the result of contracted lung, massive atelectasis, a sequela of compressed lung from long-continued pneumothorax. Figure 9 (bottom) represents an electrocardiogram made December 1935 and is very similar to the record of December 1932. There is depression of the RST and inverted T_1 and $_2$. The electrocardiographic changes are not unlike those frequently observed in hypertensive heart disease although there is no roentgenological evidence of cardiac enlargement.

Discussion

The QRS, RST, and T-waves are subject to many variations caused by change of potential within the heart muscle. Factors responsible for such changes in the QRS group, according to Pardee,[3] are: (1) The normal variations in the structure and distribution of the terminal arborizations of the auriculoventricular bundle inside the two ventricles. (2) Position of the heart within the thorax. (3) The relation of the weight of the muscle masses of the right and left ventricles. The RST segment and T-wave show normal variations depending on the changes in electrical potential resulting from the degree of change in position of the heart during systole, and the variation in the rate of relaxation of the ventricular muscle.

The presence of Q_1 is considered as indicating coronary disease when[5] it "measures at least 1 mm. and is at least ⅕ as large as the largest R deflection in any lead, and in which there is a definite R-wave in Lead I measuring less than 5 mm. in amplitude." Pardee[4] has recognized the Q_3 as indicative of coronary disease when it measures 25 per cent or more of the largest amplitude of the QRS shown in any one lead. Twelve of the 416 cardiograms studied show a Q_3 which conforms to the standards set forth by Pardee.[4] Two of these patients were obese, with high diaphragms[11]; five showed an elevation of the left diaphragm associated with

narrowing of the left lung field, and pleural thickening; one case showed an elevation of the right diaphragm secondary to phrenic nerve evulsion; one case, arterial hypertension; one case, a progressive tuberculous lesion with extensive cavitation showed only a transitory Q_3; the remaining two cases had possible mediastinal adhesions. There were two cases that showed a Q_2 and Q_3 which conform to the standards outlined by Durant [5]; one of these showed quite pronounced coronary sclerosis at post mortem. There was no autopsy in the other case. None of these patients presented symptoms suggestive of an anginal syndrome. The question is raised as to the influence of change in position of the heart upon the occurrence of Q waves, especially in those patients presenting definite evidence of elevation of the diaphragm.

Electrocardiograms of the Q_1 type conforming to the standards as set forth by Durant [5] were found in five instances. Three of these occurred in cases showing definite shifting of the heart to the left, one in shift to the right, and one in no shift. None of these cases presented a typical anginal syndrome, and the cause for the Q_1 was undetermined.

Slurring or notching of R or S with no increase in the QRS interval was noted in 56 or 15 per cent of the normal and subnormal arterial tension cases, and in eight or 20 per cent of the hypertension cases. There are 27 records which show the R- and S-waves approximately equal in amplitude in two leads with an R and S present in the third lead.[12] Pardee [6] called attention to this peculiarity and advanced an opinion that such an arrangement does not occur in records from normal hearts. An opinion from the author as to the pathological significance would be of little value. It is believed to indicate myocardial disturbance of some type.

Thirty graphic records in this series, 7.2 per cent, are tabulated as indicating intraventricular block. Only three of these cases showed a typical bundle-branch block, two left and one right. In 13 of this group the electrocardiograms appear to meet the requirements for atypical bundle-branch lesions as outlined by Dr. Henry T. von Deesten and Dr. Moses Dolganos while 14 of them show an increased duration of the QRS interval without the prolonged notched S-wave. The average age of patients in this group of intraventricular block was 39.4 years. Considering the age, this appears to be a rather high percentage of disturbance in intraventricular conduction. The increased duration of the QRS indicates a delay in the spreading of the contraction waves over the ventricles. In the typical bundle-branch lesions it is believed that the delay in spreading of the contraction wave is due to the necessity of the conduction impulse to spread from one ventricle to the other instead of simultaneously spreading through the right and left branches of the bundle. The atypical bundle-branch block is also indicative of serious myocardial damage causing a disturbance in conduction. The increased duration of the QRS interval, without associated abnormality as found in bundle-branch lesions, is not believed to be due to thickening of ven-

tricular muscle because in these tuberculous cases there is little if any evidence of ventricular hypertrophy. Wilson and Herman [8] expressed the opinion that the increased duration of the QRS was not always due to increased thickness of the ventricular wall. The clinical picture in this series of cases, regardless of the degree of disturbance in the QRS, was very similar. In one of the cases classified as typical bundle-branch block, there was a history of an anginal attack which may have been due to coronary thrombosis. The history was negative for the anginal syndrome in the other two cases. In one case with an atypical record the postmortem findings showed a definite coronary sclerosis. The history suggests a possible anginal syndrome in two cases, but was negative in all others. In those cases showing a simple increase in duration of the QRS interval there were two with subjective symptoms of angina. It seems reasonable to assume that the disturbance of conduction may be accounted for by a disturbance of the circulation in the bundle-branch tissues.

Electrocardiograms of 43 cases, 10.3 per cent, were recorded as showing abnormalities of the RST segment. Pardee first called attention to inversion of the T deflection and also to the associated changes of the RST segments in coronary thrombosis. Parkinson and Bedford [9] discussed the characteristic serial changes in the RST segment and the T-wave, and classified them as of T_1 and T_3 type. In our series there was only one case presenting the T_1 type, and none the T_3 type. One case showed elevation of RST_2, associated with inverted $T_{1, 2}$ and $_3$; one case, depression of RST_2 and $_3$ with inversion of T_2 and $_3$. In all other instances there was simple elevation or depression of RST without associated inversion of the T. Ten showed depression of RST_2 and $_3$, 12 elevation of RST_2 and $_3$, five elevation of RST_2, two depression of RST_2, one elevation of RST_1, and one elevation of RST_3.

Graybiel and Paul White [10] in their discussion of the inversion of the T-wave in Lead I or II of the electrocardiogram in young individuals, with neurocirculatory asthenia, with thyrotoxicosis, in relation to certain infections, and following paroxysmal ventricular tachycardia state: "The T-wave is much less stable than the other electrocardiographic deflections. Although its mechanism is obscure, we are familiar with certain secondary factors which may change its form and direction. Chief among these are alterations of coronary circulation, disturbances of nervous origin, the action of toxins or drugs, and change in the position of the heart." In this series, we have tabulated six records showing inversion of T in Leads I and II, and 18 showing inversion of T_2 and $_3$. There were 70 records showing low voltage of T. In this group, we considered the low voltage of T only when the T-wave showed an amplitude of less than one millimeter in all leads. It is difficult to evaluate the significance of this abnormality of the T. The far advanced terminal cases presenting the usual evidence of nutritional disturbance, with extensive pulmonary lesion, in many instances

show low voltage of T; however, this is not universally true. A number of cases were observed which were of the well nourished ambulant type with a moderate degree of pulmonary involvement which showed a low voltage of T at all times. It appears, therefore, that the low voltage T is not a positive indication of myocardial weakness, and should be considered only in connection with abnormalities of the QRS group.

Summary

The electrocardiogram of 189 hearts, 45.5 per cent of the total number of active pulmonary tuberculosis cases studied, showed significant changes in the QRS, RST, or T deflections. Included in the eight case reports presented, there is a Q_1 which appears to meet the requirements set forth by Durant [5] as an indication of coronary disturbance; a Q_3 measuring 25 per cent or more of the largest deflection of the QRS shown in any one lead suggested by Pardee [4] as indicating coronary disease; another record showing an R and S of approximately equal amplitude in two leads with predominant S_1 and an abnormal ST_2 and $_3$. The fourth case shows, in addition to Q_1, an intraventricular block. The next case shows an increased duration of the QRS with an elevated RST_1 and $_2$. The sixth case is especially interesting because the record is practically normal until the patient suffered a sudden spontaneous atelectasis which caused a shifting of the heart to the right. The record made subsequent to this accident showed a flattening of the T in all leads, also a depressed RST_2 and $_3$. The "staircase" ST in this cardiogram is not unlike those recorded by McGinn and White [13] associated with acute *cor pulmonale*. The record of the next case appears a bit unusual in the absence of a clinical picture of coronary disturbance or evidence of cardiac enlargement. Case 8 is one of severe arterial hypertension showing a not unusual picture of depressed RST_2 and $_3$ in conjunction with an inverted T in the same leads. The interesting feature in this case is the marked distortion of the mediastinum, secondary to contraction of the right lung (atelectatic). This patient is living and presents the usual picture of hypertensive disease. It is interesting to speculate on the relation of the cardiac displacement to the hypertension.

The average age in this group of cases is probably higher than in any known group previously reported. The average duration of the pulmonary lesion, not possible to compute accurately, is estimated at approximately 15 years. So it may be said that these men are naturally approaching the "heart age." Interesting electrocardiographic changes, however, have been observed in patients between 30 and 35 years of age.

It is suggested that the abnormalities of the QRS, RST, and T-waves noted in a large percentage of this group may be due to a chronic nutritional disturbance of the myocardium incident to pulmonary tuberculosis; that there is present in the soft, flabby heart a deficiency of the coronary circulation resulting in an impairment of conduction similar to the disturbance

caused by coronary sclerosis. Dilatation and associated hypertrophy of the right heart, directly the result of the long-continued strain due to increased pulmonary resistance, may be responsible for changes in the RST segment or T-wave. There are other factors such as cardiac displacement, pleuropericardial adhesions, tuberculous pericarditis, elevation of one diaphragm, and possibly other anatomical or pathological changes which cannot be overlooked as contributing or causative agencies. The cause of these electrocardiographic changes in pulmonary tuberculosis has not been proved. The subject apparently deserves further investigation.

Conclusions

1. Four hundred and sixteen cases of active pulmonary tuberculosis and 44 inactive were studied. The cases were classified according to anatomical position of the heart; 47 showed shift of the heart to the right, 119 to the left, and 250 no shift of heart.

2. Thirty-eight of the active cases showed an arterial hypertension, none of the inactive cases.

3. One hundred and eighty-nine, or 45.5 per cent of the total number of active cases studied showed significant changes in the QRS complex, the RST segment or the T-wave. None of the inactive cases showed any important abnormality of the electrocardiogram.

4. There were 19 graphic records which showed an abnormal Q-wave, 12 of these of the Q_3 type described by Pardee. Thirty cases showed intraventricular block, 43 abnormality of the RST segment, and 119 abnormal T-waves.

5. The electrical axis is apparently influenced by the rotation of the heart on its longitudinal axis.

6. The percentage of cases showing an increase in the duration of the QRS depression and elevation of the RST with T-wave changes is higher than expected and suggests that the nutritional disturbance of the myocardium found in pulmonary tuberculosis of long standing may produce a similar electrocardiographic picture to that found in coronary disease.

7. The electrocardiogram is of value in the diagnosis of cardiac lesions associated with pulmonary tuberculosis. It is frequently the only positive evidence of myocardial disturbance.

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COMMON GASTROINTESTINAL EMERGENCIES AND THEIR MEDICAL ASPECTS *

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Diseases or disorders which may give rise to gastrointestinal disturbances of sufficient gravity to constitute an emergency may be roughly classified as follows: (1) acute inflammatory diseases of the abdominal viscera and their complications, such as peritonitis, obstruction, intussusception, torsion, perforation and abscess formation; (2) complications involving chronic lesions, especially of the upper part of the digestive tract; the most important of these are acute perforation, obstruction and hemorrhage; (3) disease or dysfunction of extra-abdominal organs in which the symptoms are predominantly of gastrointestinal nature, and (4) complications which arise during treatment or follow operation and which are chiefly toxic or mechanical in nature.

In a consideration of the various entities comprised in this classification the rôle of the physician is especially important not only in the diagnosis but in the treatment of the emergency states, whether independently or in collaboration with the surgeon.

The "Acute Surgical Abdomen"

Symptoms usually characteristic of a gastrointestinal emergency are severe abdominal pain, protracted vomiting or diarrhea, massive hemorrhage, painful distention with or without visible peristalsis, or a variable combination of these symptoms. Prostration, shock, tetany, and even delirium and coma may coexist or supervene.

As the physician is usually the first to see the patient, upon him is placed the grave responsibility of as prompt and accurate an appraisal of the situation as circumstances permit, and of securing without delay surgical consultation when it is indicated or when any reasonable doubt exists. The physician must be as mindful as the surgeon of the rapidity with which disastrous changes can occur in the abdomen and of the factor of delay or indecision, which too frequently allows an acute abdominal emergency to become an abdominal disaster. Severe pain of gradual or sudden onset usually dominates the picture. When this is associated in whole or in part with such significant signs and symptoms as localized tenderness, muscular rigidity, distention, nausea and vomiting, leukocytosis and fever, the situation is one that usually requires prompt surgical intervention.

The nature of such lesions and their diagnostic and surgical aspects

* Read before the annual meeting of The American College of Physicians, New York, New York, April 8, 1938.

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recently have been summarized in an instructive article by Abell. With such lesions, exclusive of their diagnostic aspects and symptomatic and supportive treatment, we, as physicians, are not so directly concerned. Possibly, exception may be taken in three instances: (1) that form of subacute (protected, forme fruste) type of perforated ulcer which, at the outset, closely simulates acute perforation, in nature, if not in degree, but from which the patient usually recovers without surgical interference; (2) those instances of acute gastritis or gastro-enteritis which also may simulate acute perforation of an ulcer and acute appendicitis, as has been emphasized recently by Klostermeyer and by Dietrich, and (3) acute pancreatitis, in which the mortality following operation appears to be considerably higher than that following conservative measures, as has been pointed out by a number of observers in recent years.

When the nature of an acute abdominal seizure has not been determined, it is the universal custom to withhold opiates until one reaches the decision that operation is contraindicated or is to be temporarily postponed. Guerry's statement that "morphine puts two people to sleep, the patient on the one hand and the doctor on the other" tersely expresses the reason for such custom.

By and large, this is probably the safest procedure to follow if suffering and shock are not too great. On the other hand, such a competent and experienced internist as the late Harry Singer, on the basis of observations made by Hildebrandt and Zierold, advocated the *intravenous* administration of ¼ grain (0.016 gm.) of morphine sulfate or $\frac{1}{20}$ grain (0.003 gm.) of dilaudid, if, on account of the severity of the pain, it is difficult or impossible to secure the patient's coöperation in obtaining a satisfactory history or in making a proper physical examination. However, before morphine or dilaudid is given, a sketchy anamnesis is obtained, a preliminary physical examination is made, and the *observations* are *recorded*. After administration of morphine or dilaudid in such a manner, relief is prompt, the abdomen is relaxed, and the hyperesthesia is more or less eliminated. With a fair degree of accuracy the examiner can then determine (1) the location of the point of maximal tenderness, (2) the degree of tenderness, and (3) the presence or absence of any abdominal mass. Observations made before and after morphine has been administered then can be reviewed. Suffering, exhaustion, and shock are greatly reduced and this renders the patient a better operative risk than he otherwise would be.

This method has much to commend it and although it has certain disadvantages they are by no means insurmountable. When the patient is relieved he may decline to undergo a laparotomy or may suggest that it be delayed. Therefore, the patient or his relatives must be informed of the selective action of the opiate on the pain and of its failure to influence the course of the disease. Also, in the presence of a mechanical obstruction, the very active peristalsis heard synchronously with the height of the paroxysm of pain may disappear. But, by reverting to information re-

corded prior to administration of the opiate, the physician will not be deprived of any useful data. Such at least is the opinion of those who advise that morphine should be given intravenously early in the period during which diagnosis is being attempted.

Emergency States in the Course of a Chronic Lesion of the Upper Part of the Digestive Tract

Obviously, symptoms of sufficient gravity to assume the proportion of an emergency in the presence of a chronic abdominal visceral lesion are largely the result of such common complications as acute perforation, hemorrhage, and obstruction. Acute hepatic insufficiency, hemorrhagic diathesis, and circulatory collapse following abdominal paracentesis may somewhat less frequently constitute emergencies, complicating the course of disease of the biliary system.

Acute Perforation. An ulcerating lesion of the stomach or duodenum which undergoes acute perforation usually is chronic; it is the perforation that constitutes the acute process. In such cases this complication could logically be included in the group of acute abdomens already discussed. Perforations occur two or three times more frequently among men than among women. While chronic perforation of long-standing lesions is a common complication, acute perforation occurs in only approximately 5 per cent of the cases. Such lesions are usually situated on the unprotected anterosuperior wall of the stomach or duodenum near the pylorus. Although acute perforation occurs less frequently than does hemorrhage or pyloric obstruction, it is the most frequent cause of death, followed by hemorrhage and obstruction in the order named. Evidence of a preexisting ulcer often makes possible successful recognition of this catastrophe. Graham regarded three symptoms as indicative of perforation: (1) association of pain and tenderness, (2) one point of maximal tenderness, and (3) aggravation of distress on turning over. In questionable cases an ordinary exposure to roentgen-rays centered on the dome of the diaphragm usually will reveal small collections of gas. In the differential diagnosis one must, of course, consider acute appendicitis, acute hemorrhagic pancreatitis, and acute coronary occlusion. The treatment of acute perforation is always surgical and the mortality rate should not exceed 5 per cent if operation is performed within eight hours after perforation has occurred.

Massive Hemorrhage. Massive hematemesis or melena, or both, which have their origin in gastroduodenal ulceration, are the cause of death of 13 to 30 per cent of patients who are admitted to large charity hospitals because of such hemorrhage. In general practice it is estimated that the mortality rate does not exceed 3 per cent. The incidence of death during or following the first hemorrhage of severe proportions ranges from 9 to 15 per cent. Duodenal ulcer is the commonest source of such hemorrhages, although the tendency to bleed is associated more markedly with gastric ulcer which,

however, is encountered clinically 10 times less frequently than the former. Other less frequent sources of massive hemorrhage are anastomotic (jejunal) ulcer, carcinomatous gastric ulcer, chronic hypertrophic gastritis, benign neoplasm of the stomach or small intestine, ulcer in a Meckel's diverticulum, and ruptured varices in the lower part of the esophagus or in the stomach which are associated with portal cirrhosis or splenic anemia.

Authorities generally are agreed that age is the greatest factor affecting prognosis. Postmortem findings in the majority of the fatal cases reveal erosion of a sclerosed vessel in the base of a chronic penetrating, or perforated, indurated ulcer, usually on the posterior wall of the duodenum or on the lesser curvature and posterior wall of the stomach. While treatment of profuse hemorrhage is chiefly of a medical nature, it is my opinion that the middle-aged or elderly patient who harbors a chronic lesion should be submitted to operation without unnecessary delay if he has bled on previous occasions, if he does not respond favorably to adequate treatment, as indicated by blood pressure, pulse rate, concentration of hemoglobin, erythrocyte count, and concentration of blood urea (all estimated at stated intervals), and if, in addition, he shows signs of shock, or if hemorrhage recurs at short intervals in spite of such treatment.

The profession is by no means in accord as to the best methods of treatment. There are those who stress the importance of avoiding dislodgment of the clot; they are strenuously opposed to phleboclysis, early feedings, gastric lavage for any reason, and intubation. Others stress the importance of avoiding digestion of the clot, or counteracting hemorrhagic shock; therefore, transfusions, continuous drip treatment and feedings at early and frequent intervals are advocated. In my experience the time honored custom of administering opiates, preferably dilaudid with atropine, hypodermically, the transfusion of 250 c.c. of blood at frequent intervals, the application of a partly filled ice bag to the abdomen, and the usual measures directed to the treatment of shock, if present, has proved the most satisfactory procedure. However, the consistent, good results attending the use of Witts' modification of the Meulengracht method of early and frequent feedings have influenced us to shorten considerably the period of enforced abstinence from food in these cases.

In recent years, a number of observers have pointed out that massive intraintestinal hemorrhage gives rise to certain derangement in the functions of the organism, which is characterized chiefly by marked elevation of the value for the blood urea (extrarenal uremia), a decrease or cessation of excretion of sodium chloride in the urine, urobilinuria, and a decrease in the concentration of serum protein. Increase in the concentration of blood urea is the most constant symptom; it appears within a few hours following the hemorrhage and persists for a variable period. In spite of the achloruria, the concentration of plasma chlorides may be normal or even increased. The mechanism underlying this phenomenon is still a matter of dispute. When the greater part of the blood is vomited and little reaches

the intestinal tract, these biochemical changes do not occur; thus, the presence of blood in the intestinal canal is an essential prerequisite for development of the increased concentration of blood urea. Christiansen is convinced that these changes, when present, have definite prognostic and therapeutic implications.

High Intestinal Obstruction. Undue retention of gastric contents as the result of mechanical hindrance at the pyloric outlet from inflammatory, cicatricial, or neoplastic gastroduodenal lesions, or as the result of motor impairment of the gastric musculature in the presence of lesions which cause only partial occlusion is a common complication. At least, in cases in which the condition has been verified surgically, actual obstruction or gross impairment of emptying of the stomach occurs in from 26 to 30 per cent of cases of benign lesions of the stomach or duodenum and in from 41 to 54 per cent of cases of gastric carcinoma. Cicatricial and neoplastic obstructions are unyielding but obstruction of an inflammatory nature is frequently relieved by proper treatment.

As nausea and vomiting, dehydration and prostration of emergency proportions are common to a wide variety of disorders, as will be shown, too much reliance cannot be placed upon these signs per se in the diagnosis of obstruction. However, vomitus that is suggestive of retention, visible gastric or intestinal peristalsis, undue retention of a barium meal in the absence of migraine or the inhibitory effects of morphine, are trustworthy signs of obstruction. Roentgenologic examination frequently determines the level of the obstruction and its nature. One should remember that rather high-grade obstruction or motor dysfunction may be present in the absence of vomiting, and that on the other hand, marked vomiting may be present in one clinical variant of nonobstructing duodenal ulcer (ulcus à forme tabetique), usually to the exclusion of all other symptoms and signs characteristic of the disease.

It is now a matter of common knowledge that a severe, even fatal, toxemia frequently occurs in association with a marked or long-standing high intestinal obstruction. In such cases timely recognition and correction of the toxemia has done far more to reduce surgical mortality in the past 15 years than has any other single procedure. As this, or somewhat similar intoxication occurs in a wide variety of conditions, the subject will presently be discussed at greater length.

Emergency States in the Course of Disease of Extra-Abdominal Organs

The extra-abdominal causes of severe abdominal pain, nausea, vomiting, and diarrhea are legion and no one is more aware of that fact than the experienced internist who has perspective and a background of broad training. In the hope of reducing diagnostic error to a minimum, certain procedures compatible even with an emergency can be carried out, namely: (1) ap-

praising the evidence deduced from the immediate history, complete physical examination, temperature, pulse rate, blood pressure, leukocyte count, and chemical and microscopic examination of the urine; (2) obtaining details of habits, previous illness, and symptoms antecedent to the present acute illness; (3) carrying out with dispatch certain biochemical, serologic, electrocardiographic, or roentgenologic examinations in the presence of atypical or complicated conditions. Fortunately, the first two procedures supply the necessary information for adequate diagnosis of the majority of abdominal emergencies.

Pneumonia. Abdominal pain and increased tension of the upper portion of the rectus and oblique muscles, which occasionally are associated with lobar pneumonia or with pneumonia that involves a lower lobe that is complicated by diaphragmatic pleurisy, may be mistaken for acute appendicitis, especially among children. Such conditions among adults may excite suspicion of leaking duodenal ulcer or acute cholecystitis. Mistakes can be avoided by repeated physical examination and by roentgenologic examination of the lungs whenever necessary.

Angina Pectoris and Acute Coronary Occlusion. The occasional epigastric situation of the severe paroxysmal pain of angina pectoris, and the severe oppression or agonizing pain of sudden coronary occlusion is often difficult to distinguish from the pain of perforated ulcer, biliary colic, acute pancreatitis, or mesenteric infarction.

Helpful in differentiation of these conditions, briefly stated, are the following features: (1) the nature of the antecedent history and of the symptoms and signs observed during a seizure; (2) the age and sex of the patient; the vast majority of the victims of coronary accidents are middle-aged or elderly men; (3) the nature of the electrocardiographic, cholecystographic and roentgenographic findings. Sometimes the coexistence of a lesion in the thorax and in the abdomen adds to the diagnostic perplexities. Willius has pointed out, for example, the frequent coexistence of coronary disease with disease of the biliary tract, both of which contribute to the symptoms and signs presented.

Pelvic Disease. In the reproductive period of life acute abdominal pain may be the result of ruptured ectopic pregnancy, acute pelvic peritonitis, or rupture or torsion of an ovarian cyst.

Emergencies Associated with Disease of Some of the Ductless Glands

Diabetic Acidosis and Coma. Abdominal pain, gastrointestinal disturbances, fever and leukocytosis are present in about 75 per cent of cases of diabetic acidosis before coma supervenes, according to the observations of Bothe and Beardwood. Vomiting by a known diabetic is always of serious import and should never go unheeded. When in doubt, tests for urinary sugar can be carried out in the home, and for diacetic acid with

ferric chloride. If coma threatens or supervenes, prompt intravenous administration of insulin and physiologic saline solution to replace excessive loss of fluids and electrolytes is indicated, because the promptness with which treatment is carried out is one of the most important factors in prognosis. As soon as possible, the patient should be transferred to the hospital where the important determinations of blood sugar and carbon dioxide combining power of the plasma can be made from time to time and adequate therapeutic procedures instituted.

Hypoglycemia. In this condition, whether induced or spontaneous, hunger, nausea and vomiting may be prominent symptoms. In certain instances upper abdominal pain is present. This condition is usually encountered among diabetic patients who have taken too much insulin; but the cases of spontaneous origin are more apt to give rise to diagnostic difficulties. Emergency measures consist of the administration of a solution of dextrose; it may be given by mouth in milder cases but if the patient is comatose it should be given intravenously. If a sterile solution is not available a dilution of common corn syrup may be given by stomach tube.

Acute Adrenal Insufficiency. This so-called addisonian crisis is relatively uncommon but is an exceedingly dangerous state of affairs. Such a crisis may be difficult to recognize if the symptoms and signs characteristic of Addison's disease (buccal pigmentation, hypotension, asthenia) are not prominent. Nausea, vomiting, and abdominal pain are striking early symptoms. There are marked changes in the physiochemical constituents of the blood, such as anhydremia, increase in blood urea and nonprotein nitrogen, marked reduction in the values for total base, plasma chlorides and serum sodium, and an increase in the concentration of serum potassium. The treatment consists of the administration of potent extracts of adrenal cortex, the injection of physiologic saline solution to which has been added sodium citrate or a similar sodium salt, and a diet that is low in potassium.

Crisis of Exophthalmic Goiter. Anorexia, diarrhea and protracted vomiting, along with restlessness and psychic disturbances, are the chief features of this crisis. If the usual signs and symptoms of exophthalmic goiter are not prominent, the cause underlying the marked gastrointestinal disturbances may be misinterpreted. Laboratory studies furnish little assistance. The treatment consists of frequent repeated doses of compound solution of iodine (Lugol's solution), as much as 10 minims (0.6 c.c.) every 15 to 30 minutes, taken in milk, grape juice or water, during the first 24 hours, and 30 minims (2 c.c.) daily thereafter for three or four weeks. The intravenous administration of dextrose and physiologic saline solution is helpful because the patients are usually severely dehydrated.

In a recent more detailed article concerning the diagnosis and treatment of the emergencies associated with disease of the ductless glands, including the parathyroids, Kepler made this significant statement: "It is a curious and unfortunate fact that in the first four of these conditions, gastrointes-

tinal symptoms may be conspicuous and consequently may overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault."

Complications Arising During Treatment of or Following Operation on the Digestive Tract

Extrarenal Uremia (Alkalosis, Hypochloremia, Azotemia). We have already observed how hemorrhage, high intestinal obstruction, and disease of certain ductless glands may produce biochemical changes of sufficient degree to constitute a grave emergency. Dehydration, disturbance of the acid-base equilibrium of the blood, increased breakdown of endogenous proteins, oliguria, and probably temporary dysfunctions of the liver and kidneys seem to be the factors chiefly instrumental in bringing about this form of toxemia. The disturbance of water and inorganic salt balance is of primary importance, and clinical experience has repeatedly shown that it can be brought about by a wide variety of causes which may be both functional and organic in nature. Intractable vomiting of hysteria or psychoneurosis, acute alcoholism, acute gastroenteritis, hyperemesis gravidarum, the marked loss of gastric juice resulting from vomiting, from repeated gastric lavage, from continuous suction or from duodenal fistula, and the loss of body fluids as the result of a severe diarrhea, salt poor diets in renal and cardiac disease, hepatic disease, and induced severe diuresis may precipitate as severe a toxemia as that induced by high intestinal obstruction. The administration of alkalies to patients with peptic ulcer who for one reason or another are susceptible to the drug will bring about the same effect. Curiously enough, regardless of the wide diversity of causes, the morbid physiochemical changes in the organism are practically identical, namely, a rise in the concentration of urea and nonprotein nitrogen in the blood (uremia), a reduction in the plasma chlorides (hypochloremia), an increase in the carbon dioxide combining power of the plasma (alkalosis), and dehydration.

The diagnosis is based on the toxic manifestations and on the chemical examination of the blood. When patients are treated with alkalies the first symptoms are a distaste for milk, headache of variable severity, metallic after-taste, nausea, vomiting and vertigo, and frequent intensification of all these symptoms after the patient has taken an alkaline powder. As the intoxication progresses, irrespective of the original cause, whether functional or mechanical, one observes a flushed face, increasing nervous irritability, anxious expression and dehydration. In extreme cases there are incoherence, semiconsciousness and tetany. Delirium, coma and death may result if proper treatment is delayed.

Intestinal obstruction at a level lower than the jejunum also gives rise to azotemia and dehydration, but with a normal concentration of the plasma chloride and a variable acid-base equilibrium. This was observed by

Falconer and Lyall in 13 cases of obstruction of the small intestine and in six of obstruction of the large intestine. Acidosis of a nondiabetic and nonnephritic nature was observed in eight cases. In order to correct a seriously decompensated alkalosis and dehydration, for the past 15 years we have resorted to the intravenous administration of a 1 per cent solution of sodium chloride and 5 to 10 per cent solution of dextrose in 1000 c.c. of freshly distilled water, one to three times daily. The amount varies with the degree of toxemia, as indicated by the degree of chemical change in the blood. Ringer's solution in the amount of 80 to 100 c.c. per kilogram of body weight is a good substitute, especially if it is necessary to administer the fluid subcutaneously or intraperitoneally.

In the treatment of acidosis, which occasionally is encountered in cases of obstruction of the lower part of the small bowel and colon, in advanced stages of hepatic cirrhosis, in severe diarrhea, in fistulas of the small intestine and biliary ducts, 100 c.c. per kilogram of body weight of a mixture of isotonic sodium r-lactate, and isotonic or slightly hypotonic Ringer's solution in the proportion of 60:40 as recommended by Hartmann, has proved effective. Ringer's solution alone is useful. Kirk prefers an isotonic (1.3 per cent) solution of sodium bicarbonate. The dose of sodium bicarbonate necessary to restore the alkaline reserve to normal values can be calculated rather accurately by means of the nomogram of Palmer and Van Slyke. The daily urinary excretion should amount to 1500 c.c. to insure adequate renal function. Maddock and Coller recently have shown that a dehydrated patient requires at least 5000 c.c. of fluid daily. Where circumstances permit, as much fluid as possible should be given by mouth, the remainder should be given rectally or parenterally.

Hypoproteinemia and Gastric Retention. In certain gastrointestinal disorders there may be an inadequate intake of protein or an inadequate absorption of ingested protein from the gastrointestinal tract with resulting reduction in the level of the serum proteins and of the colloid osmotic pressure which they exert. "War edema" and "prison dropsy" and the anasarca that frequently occurs in sprue and certain diarrheas are examples of nutritional edema. It is a well-known fact that hypoproteinemia may occur in hepatic cirrhosis and that the low concentration of serum proteins often is intimately related to the formation of edema and ascites.

Hypoproteinemia can cause malfunction of a stoma following a Billroth I or Billroth II procedure, or after a gastrojejunostomy for obstructing duodenal ulcer. It thus may cause marked impairment of gastric emptying and subsequent toxemia. Recent observations by Jones and Eaton, Barden, Ravdin and Frazier, Mecray, Barden and Ravdin disclose the fact that hypoproteinemia and edema of the gastric mucosa must be considered as possible causes of such retention in cases in which a faulty surgical technic is highly improbable. According to Falconer and Lyall, this edema may be easily aggravated by the injudicious administration of saline solutions. They have estimated that 15 to 20 Gm. of sodium chloride daily are adequate to

correct chloride deficiency. This may be given as 1500 to 2000 c.c. of 1 per cent solution of sodium chloride. Any additional fluid required may be administered orally, rectally or parenterally in the form of a 5 per cent solution of dextrose. These authors further observed that the intake of salt should be restricted to 10 Gm. daily (1000 c.c. of 1 per cent solution) if the value for the plasma chloride approaches to 550 mg. per 100 c.c. The diminution in osmotic pressure as the result of decreased concentration of plasma chlorides probably accounts for the tendency to edema which arises when the tissue reserves of chloride are raised. Coller, Dick and Maddock have shown that edema is more the result of the administration of excessive amounts of sodium chloride than of large quantities of water. A high protein diet and transfusions are important factors in raising the concentration of the serum proteins.

Summary

A wide variety of diseases and disorders frequently gives rise to disturbances predominantly of gastrointestinal nature and of sufficient severity to constitute an emergency. Differentiation of an acute abdominal condition that requires prompt surgical interference and a nonsurgical one is the most important function of the physician.

In chronic lesions of the digestive organs the more common complications, perforation, hemorrhage, and obstruction, frequently give rise to conditions which constitute an emergency. Serious disorders engendered by disease remote to the abdominal organs, those of pulmonary, vascular and incretory systems in particular, are chiefly of a gastrointestinal nature and frequently overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault.

Toxemia, variously designated as extrarenal uremia, hypochloremia, azotemia, alkalosis, or nondiabetic acidosis, is a frequent occurrence and constitutes an emergency incident to certain forms of treatment, preoperative states, or postoperative complications. Of less frequency and gravity is hypoproteinemia, an important cause of edema and postoperative impairment of gastric motor function. The successful management of these common gastrointestinal emergencies necessitates their timely recognition and the prompt institution of adequate therapeutic measures.

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CLINICAL OBSERVATIONS, COMPLICATIONS, AND TREATMENT OF ACUTE UPPER RESPIRATORY TRACT INFECTIONS *

By Arlie V. Bock, M.D., *Cambridge, Massachusetts*

Notwithstanding the fact that medical literature abounds with discussions concerning acute upper respiratory tract infections, one need not apologize for bringing the subject to the attention of this audience. Roughly speaking, these infections account for about 50 per cent of the time lost from work in this country (Brundage (1928 [1])). Dochez [2] makes the statement that "epidemiological studies indicate that on the average every man, woman, and child in the United States experiences about two and one-half colds each year." While such a statement is not readily capable of proof, the fact remains that no other condition disables manpower to the extent accomplished by upper respiratory tract infections.

The present study is not concerned with epidemiology, nor with etiology, nor with pathways of infection. It deals with the care, in Stillman Infirmary of Harvard University, of 1667 cases of acute respiratory infection treated by myself and associates during the period, September 1935 to March 1, 1938. The subjects were undergraduates and graduate students at Harvard, the principal age range being from 17 to 25 years. The main purpose is to make a plea for simple treatment, the fruits of which are perhaps best indicated by the relatively small list of complications of all sorts occurring in this series.

The clinical picture in general may be characterized by the following: congestion of the nose and paranasal sinuses, mucoid or purulent nasal discharge, malaise, and often fever, cough and sore throat. We have included a few cases of simple coryza and we have made no diagnosis of influenza, since the evidence is not yet clear that the virus of influenza may act without producing the usual picture of prostration and depression characteristic of this infection. We have not been able to separate clearly the hypersensitive or allergic group among our patients, described by Spiesman and Arnold.[3] Fifty-seven cases were admitted on the day of onset following a chill, about 4 per cent of the total number. All of these had fever lasting one to three or four days, some of them showing normal physical examinations. Twenty-four per cent were admitted one day after onset, 30 per cent after two days, 17 per cent after three days, and 25 per cent after four or more days of illness. The patients in this series spent 7,708 days in the Infirmary. If we add to this the days of partial disability due to illness before admission to the Infirmary, information on which is not complete, the total of partial and complete disability is in excess of 25,000 days, a time span of

* Read at the New York meeting of the American College of Physicians, April 6, 1938.
From the Department of Hygiene, Harvard University.

TABLE I

Upper Respiratory Tract Infections, Stillman Infirmary, Sept., 1935–March 1, 1938

Total Number	Total Infirmary Days	Duration in Infirmary					
		Days 1–6		Days 7–10		Days 11+	
		Total Number	Average Stay	Total Number	Average Stay	Total Number	Average Stay
1667	7708	1400	3.6	193	7.8	74	16.4

All admissions to Stillman Infirmary during same period = 4268.
Respiratory infections = 39%.

more than 70 years. In our out-patient clinic for undergraduates, 2,632 respiratory infections were reported during the academic year, 1935–36, and 2,280 during 1936–37. Since the undergraduate group comprises about 3,700 men, there has been roughly one respiratory infection per year for 60–70 per cent of the total, considered serious enough to report. Many of these were treated either at home or by rest in their rooms.

In passing it is of interest that the curve of incidence of respiratory infections in this series, shown in chart 1, follows rather closely the curve published by J. G. Townsend.[4]

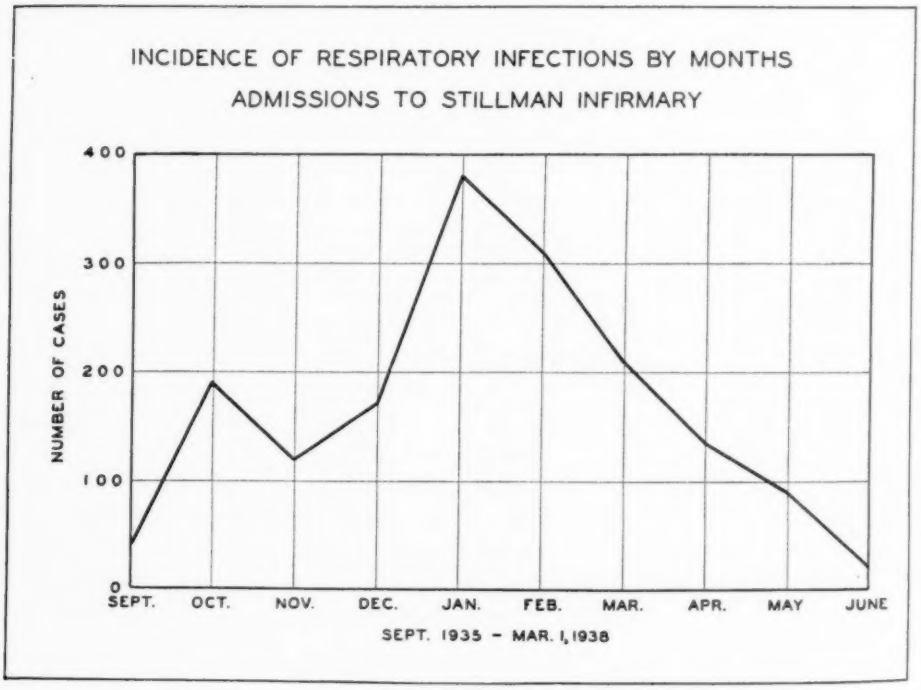

CHART I

Relatively minor variations occur from year to year in the clinical picture of the usual respiratory infections. The present series is composed for the most part of the more severe cases occurring during the period of observation. The notations included in table 2 cover only outstanding findings. Fever occurred in more than half the cases, chills in only 57 but chilly sensations were common. The complaint of aches and pains was not as frequent as is generally supposed in the syndrome usually called "grippe." Soreness of the throat was noted in 309 instances, although clinical evidence of pharyngitis was present in the majority of the cases. The diagnosis of laryngitis was restricted to the patients having partial or complete aphonia. The cases of acute tonsillitis presented the usual typical clinical picture of this infection. The diagnosis of bronchitis was not made unless the pulmonary râles characteristic of this state were present. Chronic cervical adenitis is not uncommon but the present findings are restricted to swollen tender glands presumably associated with the current infection. In certain

TABLE II
Clinical Observations

Fever One or More Days	Chills	Aches and Pains	Sore Throat	Laryngitis
881	57	109	309	83
Acute Follicular Tonsillitis	**Bronchitis**	**Cervical Adenitis**	**Toxic Erythema or Rash**	**Palpable Spleen**
28	22	195	26	28

cases, toxic erythema may closely simulate scarlet fever, but the latter diagnosis was excluded on other grounds. A few cases exhibiting a morbilliform rash required isolation because of resemblance to measles, but the rash was unaccompanied by mouth lesions and usually faded in two days or less. One case had petechial lesions beneath the clavicles and scattered elsewhere characteristic of those seen in sub-acute bacterial endocarditis.

The occurrence of a palpable spleen in 28 cases with or without accompanying adenitis in the presence of respiratory infection is new in our experience. These cases must be differentiated from cases of acute infectious mononucleosis. The blood picture for two or three days may show 20 to 25 per cent of mononuclear cells, with rapid return to a normal differential count. They probably represent cases frequently diagnosed as mononucleosis in which the heterophile reaction is negative.

White blood cell and differential counts were done in only 23 per cent of this series. The fact is mentioned here merely to point out that in the absence of known complications 35 per cent of these patients had white

counts ranging from 10,000 to 23,000. This is contrary to the usually accepted opinion that uncomplicated cases of so-called "grippe" have as a rule a leukopenic response.

We wish to lay particular emphasis on the relatively small number of major complications encountered, listed in table 3. Many of the cases of otitis media had developed before the patients were admitted to the Infirmary. The one case of mastoiditis did not require operation in the opinion of several consultants. With reference to the surgical drainage of antra, it is our opinion that this procedure is not commonly necessary. Irrespective of roentgen-ray findings showing complete clouding of one or both antra, many such cases will clear up in the course of two or three weeks with simple bed care. It would be a rare case indeed in which surgical drainage of antra should be advised or attempted until well after all other signs of the acute infection have subsided. Failure to observe a rule so simple may lead to serious trouble both present and in the future. Observance of this rule will abolish much of the necessity for the use of prontylin in the treatment of acute sinusitis. In this connection it is well to remember that the

TABLE III
Major Complications

Otitis Media		Mastoiditis	Antra Drained Surgically	Peritonsillar Abscess	Pneumonia
Secretory	Purulent				
20	9	1	2	1	52

complaint of chronic sinusitis is often an obsessive characteristic and that correction of existing maladjustments will produce more effective results than treatment directed at the local condition.

Of the 52 cases of pneumonia, only four were due to type specific pneumococci. One was due to hemolytic streptococcus. The great majority of the cases we believe represent a virus pneumonia, with partial or complete involvement of one lobe of the lungs. Spread of the process to another lobe occurred in some cases. On admission to the Infirmary these cases could not be differentiated from the usual type of respiratory infection accompanied by fever. As a rule the first evidence of the presence of a pneumonic process was obtained by roentgen-ray examination on the fourth or fifth day after admission. Further observations on this subject will be considered in another communication. One death occurred in a Boston Hospital in a case of Type I pneumococcus pneumonia, due to acute toxic nephrosis. The administration of Type I serum may have accounted for the nephrosis.

A matter of great interest is the fact that we have not encountered acute

involvement of joints in any case. If acute infectious arthritis occurs incident to upper respiratory infections, we believe it to be an uncommon sequela. During the period under consideration we have seen only two cases of acute rheumatic fever in the student body. No case of acute nephritis has developed. An attack of asthma was apparently precipitated in 10 cases, all having prior histories of asthma; hay fever complicated two cases, and diarrhea occurred in twenty.

Common-sense treatment of acute upper respiratory tract infections, including the common cold, with or without fever, requires bed care, a return to the principle established by Hippocrates. Time, trouble, and money will often be saved by the early institution of this method. Whatever the specific etiological factors may be, it appears clear to us that fatigue of body and mind in adult patients plays a rôle in the precipitation of these infections not generally recognized. The main principle of treatment should be rest. We believe that energetic local treatment produces irritation of the nasopharyngeal membranes, often prolonging the course. We do not advise the use of sprays, nose drops containing ephedrine, adrenalin packs in the nose, or painting the throat with argyrol or dyes. Through many recorded observations of the past, it has been known that the mucous membrane of the nasopharynx is especially sensitive to temperature changes and other stimuli. The present work of Drinker and his collaborators [5] is opening a new vista concerning the absorptive properties of this area. The mechanism is so complex that we do not yet know enough to assist it intelligently when the usual infections are present. That irritation is set up by the free use of ephedrine, for example, is no secret and the after-effects of surgery in the nose, of whatever kind, suggest that damage may follow that is not readily repaired. Surgery in this area at all times should be approached with caution. Our results in the present series of cases indicate that few complications result from the simple policy of instituting bed care. Salicylates and codeine are used for comfort. Laxatives are not usually prescribed. There is reason to believe on the evidence of Kerr [6] and others, that control of temperature, humidity, and dust would add greatly to the effectiveness of treatment.

That prevention of upper respiratory infections by vaccines has little to support it, has been well shown.[7, 8, 9, 10] Lacking specific means of therapy, the greatest advance on the problem at the moment would be made if we could teach ourselves and our patients how to live within our physical resources, and especially within those of our central nervous systems. Such influences as chilling of the body, weather changes, irritative substances in the atmosphere, and contagion, must be taken into account; but granting these, under ordinary circumstances, the rôle played by the tension of living must be recognized more generally in our assault on the problem.

My appreciation is acknowledged of the generous time given by associates in the Department of Hygiene in reviewing the case histories.

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CONSTITUTIONAL FACTORS IN ARTHRITIS WITH SPECIAL REFERENCE TO INCIDENCE AND RÔLE OF ALLERGIC DISEASES *

By ROBERT T. POTTENGER, M.D., *Pasadena, California*

CHRONIC arthritis of the atrophic and hypertrophic types is the most common chronic illness and ranks first among the causes of disability. The high incidence of this disease is indicated by a survey in Massachusetts where 3.2 per cent of the total population and 30 per cent of the disabled were found to be suffering from rheumatoid disease.[1] In spite of its prevalence the medical profession as a whole is discouraged or at least apathetic in its treatment.

There is no agreement among students of chronic arthritis as to the basic factors or diathesis predisposing the patient to the disease nor is there agreement as to the nature of the causative agent. The American Committee for the Control of Rheumatism stated that it "conceives of the disease as a generalized disease with joint manifestations." Yet the joint manifestations must be present to diagnose the disease.

This confusion led me to analyze my first 50 cases in which arthritis was the chief or a prominent complaint, not only from the standpoint of the signs and symptoms of arthritis but also from the standpoint of complications disclosed both in the history and physical examination. Certain relationships appeared quite striking. In the next 50 cases special attention was paid to them. An analysis of this series again suggested further studies. As a result the statistics which follow will be in part based on 150 consecutive cases, while some of the statistics will be based on separate series of 50 patients. At times this may be confusing but it is difficult to get the same data in a series of patients unless special thought is given to it.

In this paper both clinical types of arthritis, the atrophic and hypertrophic have been grouped together as it appears that fundamentally they are the same disease. However as this is not proved and time does not permit a defense of this position the series was classified as to predominant type.

Type	*Number of Cases*	*Per Cent*
Hypertrophic	95	62⅓
Atrophic	47	31⅓
Mixed	8	5⅓

There were 22 males or 14 per cent and 128 females or 86 per cent. This series is rather overloaded with females as it is generally considered that the incidence is only about twice as great among females. The average age of the 150 patients was 53.3 years.

* Received for publication September 21, 1937.

Clinical Manifestations of Arthritis

My studies lend support to the conception that arthritis is a generalized disease with joint manifestations. In the first place the symptoms as given by the patient are not confined to the joints; secondly, the general symptoms tend to precede joint symptoms or to persist during periods of freedom from joint symptoms; and finally there are definite constitutional trends shown by the group.

The first 50 cases were tabulated with regard to the major symptoms shown.

Class of Symptoms	Symptoms	Per Cent
Constitutional	Mild malaise or feeling of being less well	84%
	Of inability to sleep well not necessarily from pain	74%
	Nervousness and depression	74%
Gastrointestinal	All varieties as will be taken up later	
	Of various grades of constipation	88%
	With two or more stools a day	8%
Circulatory	Facial pallor and delayed capillary circulation in the finger tips in all active cases	
	Numbness of extremities	54%
	Cramping of muscles	32%
Skeletal	Pain	100%
	Stiffness	74%
	Swelling of joints	50%
	Weakness or atrophy of muscles	34%

It will be noted that only 50 per cent were recorded as having joint swelling. Arthritis in the spine, sacroiliac and hips will not give joint swelling perceptible on ordinary examination nor will an early joint involvement without effusion and before marked thickening of the capsule.

A study of the clinical course of arthritis as shown in the histories again illustrates the generalized character of the disease. Usually there is a history of ' never being sick but never being really well,' of constipation and of poor circulation for years before the onset of joint symptoms. We have all seen cases with well marked hypertrophic spurs who have never or have only recently had joint symptoms; an experience which forces us to the conclusion that arthritis has been present without joint symptoms. Consequently the disappearance of joint symptoms cannot be regarded as proof of the cure of the disease. The last 50 patients in the series were studied with this in mind. In 48 patients the age of onset of the first joint symptoms was noted and in 49 the age of onset of continuous joint symptoms. In 12 of 23 cases of the atrophic type and in 9 of 27 cases of the hypertrophic type the onset of the first joint symptoms and that of continuous joint symptoms were the same. Consequently 58 per cent of the cases had definite attacks of joint symptoms with periods of freedom before the onset

of continuous joint symptoms. The fact that 20 per cent of the cases were under 45 and 10 per cent had symptoms less than one year makes it probable that even a greater per cent would have remissions if followed long enough.

Constitutional Background

Certain hereditary and constitutional factors seem to furnish the soil on which arthritis develops. In 73 per cent of 150 cases there was a family history of allergic diseases and in 52 per cent a history of arthritis. In 80 per cent one or the other or both were noted. Due to the lack of specific knowledge about blood relatives these figures from the histories are more suggestive than absolute.

In the first 50 cases a definite trend to longevity was noted, so that in the subsequent 100 cases the ages of 196 of the 200 parents were obtained. One hundred five of these had died at ages over 70 or were still living at an age greater than 70. Fifteen parents under 70 were still alive. Taking their ages and using the American Men's Ultimate Mortality Table it was computed that 9 of the 15 living should reach 70. Thus 114 or 57 per cent of the parents of these arthritics live to 70. Assuming that the average age of the parents at the time of birth of the patient was 30 and using the American Experience Mortality Table for comparison we find that 45.1 per cent of people aged 30 would reach 70 and 57 per cent would reach a fraction over 65. Since longevity has been proved to be inherited arthritis may be said to have a constitutional background of longevity.

The group showed a definite tendency to low blood pressure at the initial examination, but as the group as a whole was not studied carefully and repeatedly from this point of view statistics would be misleading. However, only 4 or 2.7 per cent of the 150 patients had diastolic pressures of 100 or over. Only 2 per cent of the last 100 showed persistent albuminuria and casts and low specific gravity indicative of any considerable grade of nephritis. An analysis of the blood pressures and urinary findings indicates that arthritics develop primarily arteriosclerosis rather than hypertension and nephritis.

Focal Infection

Having found that there is a constitutional background and generalized physiological disturbances associated with the joint symptoms of arthritis we turn to the subject of focal infection. Pemberton [2] noted in one series of 545 cases of arthritis demonstrable foci in 70 per cent while in another series of 100 non-arthritics 87 per cent had demonstrable foci of infection. In this second series in a general medical ward, nephritis and cardiac conditions were the chief disease states. Thus focal infection is not a condition peculiar to arthritis. In reviewing 100 cases in which special attention was given to the history of removal of foci I found I was entering upon a well tilled field as most of the patients had had previous medical care and

87 per cent had had active disease more than one year. The figures illustrate the persistence of arthritis in spite of the absence of foci in the usual location, teeth, tonsils, sinuses, gall-bladder and appendix.

In regard to teeth 25 per cent of the patients were edentulous, 13 per cent having been so before the onset of their arthritis, 12 per cent having had all the remaining teeth extracted because of it. In another 28 per cent some teeth had been extracted because of rheumatism. A further 8 per cent were found to require dental care. The tonsils were well attended to; in 28 per cent they had been removed before the onset of the arthritis and in 27 per cent tonsillectomies had been performed for the joint symptoms. Thus in 55 per cent rheumatism persisted in the absence of tonsils. The appendix had been removed in 23 per cent and probably in 2 others who had had pelvic operations. Only 8 per cent had had nasal operations, which is noteworthy as a large number had nasal symptoms as will be shown later. Six had had gall-bladder operations. In two others there was a history of jaundice in adult life but none of colic. Many of the patients had had gall-bladder roentgen-ray studies at some time during their illness. As to genito-urinary foci one had pus in the prostatic secretion and five gave a history of urinary tract infections in the past.

These figures are given not with the intent of proving that removal of foci is of no value in arthritis but to emphasize that arthritis will persist after the usual foci have been removed. Many physicians have observed that marked benefit from the removal of foci in arthritis is rarely seen except early in the course of the disease, and these patients in my series represent the ones who were not permanently benefited by such removals.

It would be poor medicine, however, to tell a person who had an abscessed tooth that he should neglect it because careful examination brought out no evidence of any systemic pathological disturbance from it. Whether a focus of infection is the direct cause of joint symptoms or not, it may when added to other factors already operating be sufficient to upset the physiological balance of the patient and precipitate symptoms just as other infections, fatigue, meterological disturbances and menstruation will. Many of my patients gave a history of being benefited by removal of foci, many were made worse and most noticed no effect. Focal infection in arthritis presents no more urgent problem than in other diseases and should be attacked with due regard to the patient's vitality.

Frequency of Allergic Manifestations

When the first 50 cases were reviewed, the incidence of a history of asthma, hay fever, hives, eczema, bilious headaches and canker sores was very high. The incidence of asthma was 4 per cent, that of nasal allergy 20 per cent, hives 12 per cent, eczema 16 per cent, migraine 14 per cent and other sick headaches another 26 per cent, canker sores 36 per cent. It was found that 78 per cent had at least one of these allergic manifestations.

Eczema, hives, canker sores and sick headaches are generally regarded as being due to protein sensitization in which food is the offending factor, while asthma and nasal allergy may or may not be. Curiously enough I had found four of the eleven patients in whom no note was made of other evidence of allergy, sensitive to foods in the diet I was using. As was mentioned earlier 96 per cent of this first group of 50 had abnormal bowel function. The next 100 cases were studied carefully from the standpoint of food allergy.

The following table shows the frequency and distribution of the various types of allergic manifestations in the next 100 cases as noted either in the past history or the progress notes.

Nasal allergy	50
Asthma	11
Eczema	13
Bilious headache including migraine	38
Canker sores	42
Gastrointestinal	94
Bladder	17
Urticaria	13

Distribution Among Patients

Distribution among Patients

	6 Types	5 Types	4 Types	3 Types	2 Types	1 Type	None
No. Pts.	1	6	23	29	28	10	3

In two of the three cases where no allergic manifestations were noted the history was inadequate and treatment too short to determine the presence of allergic manifestations and in one case the symptoms might have been caused by an active tuberculosis, observation again being too short to be certain.

It is noteworthy that 94 of the 100 patients had gastrointestinal symptoms that were considered due to food allergy. In 6 of 8 cases where the period of observation was less than one month, a history of food disagreement was considered adequate evidence. In 88 of the remaining 92 cases of the series the presence of food allergy was proved by the precipitation of their gastrointestinal symptoms by the addition of offending foods, and the relief of the symptoms by the subsequent removal of the foods. This statement that 94 per cent of this series of arthritics had symptoms of gastrointestinal food allergy does not mean that food allergy is the only disturbance present in the gastrointestinal tract and in fact it appears at times to be conditioned by other abdominal pathologic processes.

Gastrointestinal Tract in Arthritis

At this point it would be well to review briefly the gastrointestinal symptoms present in this series. A study of the last 50 patients from the standpoint of their gastrointestinal symptoms failed to reveal any characteristic syndrome, such as is found in peptic ulcer. Perhaps the most characteristic notation was the patient's observation of gastrointestinal disturbances following ingestion of certain foods or overeating. The table below shows the incidence of the more common gastrointestinal symptoms, the first column shows the percentage in which the symptom was mild or inconstant, the second in which it was severe or of concern to the patient and the third the total per cent in which the symptom was found. Twenty per cent of the

Symptom	% Mild	% Severe	% Total
Anorexia	40	10	50
Coated tongue	42	20	62
Nausea and vomiting	32	12	44
Distress after eating	26	20	46
Belching	22	18	40
Heart burn	28	4	32
Bloating	36	18	54
Soreness and cramping	32	8	40
Flatulence	16	14	30
Constipation			86
Occasional laxative	22		
1–5 a week		20	
Daily		44	
Excessive number stools	16	8	24
Mucus in stool	32	14	46
Periodic bloody mucus	6		6

group did not complain of any severe gastrointestinal symptoms. Of the 14 per cent without constipation 10 per cent gave a history of mucus in the stools including in 8 per cent an excessive number of stools. The remaining 4 per cent complained of no symptoms referable to the gastrointestinal tract except a coated tongue. Both of these later showed disturbances due to food sensitization.

These figures indicate that arthritics as a group have gastrointestinal symptoms but of no definite pattern; their severity correlates more with the nervous instability of the patient than with the severity of the disease. Three of these patients had definite pathologic lesions; one gall stones, one an abdominal fistula with three openings into the bowel and one had had repeated attacks of diverticulitis.

My experience with gastrointestinal roentgen-ray studies has been very limited. Consequently I will quote directly from Pemberton's[3] book, "Arthritis and Rheumatoid Conditions, Their Nature and Treatment."

> The type of colon which is met with in many arthritics is characterized chiefly by a tendency to greater caliber, greater length, a more convoluted appearance and sometimes reduplication. . . . It is to be borne in mind that many apparently healthy

people harbor diseased tonsils, for example, and by the same token the bowel may be potentially the cause of disease, by virtue of faulty anatomy or dysfunction, without having as yet brought this about. The colon will, therefore, be found in a certain limited proportion of apparently normal subjects also to approximate the type here described. . . . Other departures from theoretical normality show themselves in the gastrointestinal tract as the result of roentgen-ray studies among arthritics. These are chiefly in the direction of a somewhat delayed transit of the barium meal together with more or less ptosis of the stomach and colon. It is of the highest importance to note that marked stasis may exist in the presence of apparently adequate daily bowel movements. Another outstanding feature which is encountered in a given proportion of cases is the regurgitation of the barium through the ileocecal valve.

The "marked stasis" of which Pemberton speaks can frequently be shown by giving carmine dye by mouth. This method is used in metabolic work to mark the beginning and end of the portion of the stool belonging to a certain period of the experiment. In a strictly normal bowel action definite segments of stool show the dye. In some arthritics the dye may appear in from 24 to 72 hours and continue up to 120 hours. It is uncommon to find one segment of the stool colored and the other not colored.

Discussion

An attempt has been made to show the constitutional trends and the physiological disturbances that those who suffer from chronic joint disease of the so-called hypertrophic and atrophic varieties have in common. This was done to emphasize what has been observed already that an individual arthritic suffers from ill health as well as joint pain and that his ill health is not peculiar to him as an individual but that both the ill health and joint changes are part of the same physiological disturbance. Considerable space was given to allergic manifestations. Unfortunately attaching a name to a clinically common and unimportant phenomenon tends to exaggerate its importance in our minds, and this is especially true when the same name may be used for very serious conditions. An occasional crop of hives is just as much an allergic phenomenon as a severe urticaria but not by any means of the same clinical importance though it does indicate the same constitutional trend. Not every person but a large number do show allergic manifestations. Vaughan and Pipes [4] made a survey of 500 persons and found 10.6 were frank major allergics and 49.8 per cent more were minor allergics with mild allergic symptoms in their past history. In the same journal Bret Ratner [5] states that 7 to 10 per cent of the population are afflicted with allergy. Rowe [6] found 35 per cent with allergic history or manifestations in a survey he made.

As to the mechanism of allergic reactions only the barest outline is warranted here. There appear to be two major factors. First a deficient or altered constitution on the part of the host which seems to be a derangement of intracellular digestion and second certain specific chemical and

possibly physical stimuli which will precipitate reactions in an individual because of changes brought about by the constitutional deficiency. An allergic individual is in his apparently normal physiological balance as long as contact with the antigenic substances is avoided as for example the freedom of a pure pollen hay fever sufferer at other seasons of the year.

Arthritis is coming to be looked upon more and more as an allergic phenomenon in the skeletal structure as is shown by the tremendous amount of tissue reaction in which only few or no infectious organisms can be demonstrated. Joint reaction to the streptococcus in rheumatic fever is an example of reaction to an infectious agent. The joint manifestations of scarlet fever, typhoid fever and undulant fever are other examples. Non-infectious agents causing joint symptoms may be illustrated by the joint symptoms in serum sickness. Cases are reported where foods cause effusion in joints. In chronic arthritis the agent must be active over a long period of time. Roentgen-ray changes in the bones are often not found when the first symptoms develop and their degree and type depend on the severity and duration of the reaction.

Many authors have looked upon the bowel as the chief focus of infection in arthritis. The contents of the bowel, both food and bacterial and also their breakdown products, offer an unlimited and more or less constant source of antigens for allergic reactions in joints. Normally the mucous membrane of the bowel offers a sufficient barrier to the noxious elements in the intestinal tract so that foreign proteins do not enter the blood stream in amounts in excess of the ability of the body to destroy them. Since arthritics in general show other manifestations of allergy an arthritic probably has a deficient parenteral digestion, but we must also consider whether factors are present in the bowel itself which allow an excess of foreign substances to pass through its mucous membrane to overtax an already deficient though otherwise adequate parenteral digestion. Evidence has been presented of a very high incidence of disturbance of the gastrointestinal tract in arthritis usually with stasis and accompanied by gastrointestinal food allergy.

Rowe [7] in his book "Food Allergy" (1931) discussed the relation of food to arthritis. He mentions that Talbot (1917) and Cooke (1918) suggested food as a source of arthritic pain in certain patients and that Turnbull in 1924 noted relief of arthritic symptoms on diets based on skin tests. Rowe himself reported three cases. In his discussion he favored the view that arthritis was due to bacterial allergy but felt that in some cases it might be due to foods. More recently, in 1936, W. T. Wootton [8] suggested that arthritis is an allergic reaction in joints to food or bacterial protein and that elimination diets should be used but states that allergic food reactions are rarer as age advances. G. T. Brown,[9] in 1934, suggested that the factor of food sensitization should be considered in arthritis but that bacterial allergy was more important. Thus the association of food allergy and arthritis is being recognized.

Rôle of Gastrointestinal Food Allergy

My studies on the 150 cases in this series suggest an explanation of the rôle of food allergy. A survey of the first 50 cases showed that no case that was freed from gastrointestinal symptoms and that regained apparently normal bowel function failed to gain relief from arthritis, and the converse —that those whose gastrointestinal symptoms failed to respond or became worse failed to make much improvement, or progress. Among those who improved were the ones in whom I had recognized food allergy and had eliminated the offending foods from their diet. This observation led me to investigate the problem of food allergy in the succeeding cases.

In working out an elimination diet in an uncomplicated case of arthritis the symptoms due to food allergy will usually clear up in from five to seven days both in the bowel and elsewhere; for example, in the nose, skin, lungs, etc. There is a marked improvement in the constitutional symptoms but usually not much change in the joint symptoms for another five to seven days, but then the muscle soreness and acute inflammation in the joints begin to subside leaving chiefly pain on motion, stiffness from adhesions and weakness due to muscle atrophy. Thus there is a two week cycle. Five to seven days for the bowel to become free from symptoms and five to seven more days for the acute joint reactions to subside. The subsequent introduction of an offending food in the diet is followed in from one to seven days by a return of the allergic symptoms and a few days later after the disturbance in the gastrointestinal tract is established, the joint symptoms increase. This will occur even after the ingestion of the offending food has ceased but before the gastrointestinal symptoms have subsided. Again about five days after the bowel symptoms disappear the rheumatic pain subsides. The observation that exacerbations of the rheumatic symptoms do not occur simultaneously with the development of allergic reactions to foods in other tissues of the body but tend not to appear until a well marked gastrointestinal disturbance is set up and that remissions in the rheumatic symptoms do not occur until after the gastrointestinal symptoms subside, suggest that the rheumatic symptoms are produced by antigens whose access to the joints are conditioned by the allergic reactions elsewhere, presumably the bowel.

An allergic reaction in the bowel is accompanied by disturbed motility and by edema of the mucous membrane. The increased permeability produced by the allergic reactions is suggested by a clinical observation. An individual with a bowel allergy, on a diet that agrees with him, can eat beets without the color appearing in the urine in appreciable amounts. The same individual when having an acute bowel reaction frequently will notice a pink tinge to his urine (on several occasions red enough to engender a phone call to the doctor). This observation suggests that the permeability of the bowel has been altered so that the beet pigment is allowed to pass

into the blood stream or else passes through more rapidly or possibly its digestion in the body is impaired.

Bowel allergy is known to cause constipation and stasis. Constipation and stasis are present in a large proportion of arthritics. That it produces an increased permeability of the bowel is suggested by the beet pigment observation. Thus food allergy may produce both the colonic stasis and increased permeability of the bowel which would make the colon a likely focus for infection.

Conclusion

If arthritis is an allergic reaction in joints to foreign protein, living or dead, brought to it from the blood stream, then any portal of entry may theoretically be a focus. It is intended in this paper to imply only that the bowel is the most common focus. Tolerance to an antigen is only relative and probably depends on the efficiency of the mechanism of intracellular digestion. A coexisting food allergy may depress the tolerance to other antigens and it is well known that infection, focal or otherwise, weather, fatigue or menstruation are prone to lower the tolerance of an allergic individual. Again it is not meant to say that food allergy is the only disturbance in the bowel or always the prime one. I have seen one case of pure food allergy, which was freed from symptoms on an elimination diet, return to a regular diet without symptoms after a Jackson's membrane distorting the cecum was severed. Rae Smith in a personal communication to the author stated that adhesions were an important factor in one case in eight of the severe rheumatoid type of arthritis. Dietary deficiencies may play a rôle in the lowering of the resistance of the bowel mucous membrane. My thesis is that food allergy is the most common and in many cases the most important factor in the bowel disturbance that predisposes to chronic arthritis.

Summary

In summary, arthritis is a pathological condition of the joints behind which there is a constitutional background and a widespread disturbance of the general physiology. There is an hereditary tendency to allergy, arthritis, longevity and a hereditary resistance to essential hypertension, and glomerular nephritis. It is a condition where progress may be aggravated by foci of infection in the teeth, tonsils, sinuses, gall-bladder, etc. but where progress may persist in the absence of such foci. The type of reaction in the joint suggests an allergic reaction. This is made more probable by the almost universal presence of manifestations of specific sensitization in other tissues. The presence of disturbances in the bowel due to specific sensitization to food was shown in over 90 per cent of our cases. The clinical course of exacerbations under treatment suggests that these reactions in the bowel make it more permeable and cause the body to be

flooded with an excessive amount of antigens from the bowel to which the joint structures are sensitized.

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AFFECTIVE DISORDERS IN MEDICAL PRACTICE*

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By affective disorders we mean those characterized by pathological changes in mood and disturbances of the emotions. There may also be many physical symptoms and complaints. Victims of the outspoken psychoses in this group make up 10 to 15 per cent of the patients in psychiatric hospitals. The practising physician sees these patients relatively early and when we broaden our conception of affective disorders to include those occurring in more or less natural reaction to distressing situations and to physical illnesses we should the more readily realize their importance in medical practice.

Among the commoner affective disorders are the manic depressive psychoses, reactive depressions, and tension depressions, easily recognized as emotional disturbances when the affect is obvious but how often even then misconstrued and maltreated. Mr. John Doe's wife, Mary, aged 40, has been for two months sinking deeper and deeper into a depression. She is taken to an old friend of the family, a surgeon, let us say, who after hearing the story decides to give her a good talking to. "My dear Mary," he says, "I have known you for twenty years and in all that time I have regarded you as a faithful wife, a devoted mother, and a wonderful housekeeper. You have always been looked upon by your neighbors and friends as a model in these particulars. I cannot understand what has come over you. You are making your husband's life miserable by adding greatly to his cares and worries, you have lost all interest in your household duties, and you are neglecting your children at this crucial stage in their development. Please understand that this sort of thing must stop at once." At the conclusion of the lecture the poor, miserable creature who entered the office convinced that her own life was wrecked, leaves it with the forcible suggestion that she has also ruined the lives of her husband and children and this may thereafter be a central idea in her depression. Another friendly physician may be less severe or even sympathetic but nevertheless ends his consultation with the urgent advice that she 'snap out of it,' a milder suggestion that she is responsible for the whole sad affair, a confirmation to her of the feelings of self-blame of which she was already only too conscious. Most of us of course would not take such an attitude but would sympathize briefly with the patient, encourage her to look forward to recovery, arrange a plan of living giving particular thought to protection of the patient, to appropriate occupation, with a form of psychotherapy suitable to the mental status at the time.

But there are patients in whom the diagnosis is much more difficult

* Delivered before the American College of Physicians, New York City, April 6, 1938.

and who are therefore often classed among the psychoneuroses. Among these may be some of the patients with tension depressions, or with merely the physical equivalents of a depression, headache, dizziness, palpitation, epigastric distress, constipation, exhaustion, insomnia. They may complain entirely of somatic distress and the variability of mood, loss of interests, poor concentration, inattention, indecision, self-blame, feelings of tension, panicky feelings, and suicidal ideas are found only by searching for them. Some of these patients are lost early by suicide because they are not recognized and protected. In the milder cases the physician may give the patient a measure of comfort along with careful guidance even though he may doubt his ability to shorten the duration of the illness, for usually these maladies are circumscribed with a definite onset and a definite offset, the time of which may not be predicted with any certainty.

There are psychiatrists who believe that the neuroses are primarily affective disorders, emphasizing the affect rather than the organ involved, and preferring to speak of " a neurosis with cardiac symptoms " rather than " a cardiac neurosis." These psychiatrists further believe that affective disorders can lead to organic changes. They may still further say that in many organic diseases the affect is of great importance for the symptomatology, for prognosis and for therapy.

Most of us internists have been trained from our medical infancy to think in terms of somatic pathology. Clinical observations of organic diseases and experimental procedures based on them are often capable of justification by proof. The results of psychic manifestations are very difficult of proof. Through the work of many physiologists, however (Beaumont, Cannon, Pavlov), we know and accept the demonstration that through the vegetative apparatus (the autonomic nervous system and the endocrine system) emotions can produce bodily changes in function including chemical changes in the blood. We are more or less familiar with the idea of the internal environment of the body or homeostasis as outlined by Cannon in contradistinction to the external environment so important in the social aspects of medicine. How much do we utilize these ideas that we have heard and accepted, or are they pigeonholed as merely academic ideas as far as our general concepts of disease are concerned? The whole question of emotions and bodily changes, or psycho-somatic inter-relationships, is of great interest to many physicians and I believe of great importance to all of us. The literature on this subject from 1910 to 1933 has been admirably digested and summarized in a monograph by H. Flanders Dunbar. The literature includes that of general biology, embryology, comparative anatomy, neuro-anatomy, physiology, psychology, psychoanalysis, and clinical work by surgeons, by physicians, and most of all by psychiatrists. It is interesting to note that the biologists in their philosophy approach so nearly the philosophy of the physicists. For example, McKinney is quoted to the effect that " emotion is the modification of energy (difference of potential) of the body by which the power in action of the body is aided or restrained,

increased or diminished, and that this difference of potential may be expressed both psychically and physiologically and that energy so expressed is the same in kind, though differing in organization, from that found elsewhere in the universe." This is not so different from the pronouncement recently attributed to Einstein.

It is pointed out that the review of literature reveals three distinctly different attitudes among practitioners toward the relationship of psyche and soma in acute and chronic disease. There is the organicistic bias, the psychic bias (equally falacious), and the organismal point of view of psycho-somatic unity. This third point of view has been preached for many years by the Meyer school of psychiatrists, by the psychoanalysts, and by Barker among the internists. Meyer says, "What is of importance to us is the activity and behavior of the total organism or individual as opposed to the activity of single detachable organs." F. Mohr is thus quoted, "There is no such thing as a purely psychic illness or a purely physical one, but only a living event taking place in a living organism which is itself alive only by virtue of the fact that in it the psychic and somatic are united in a unity." Bleuler thinks that the question, "physical or psychic?" is in many cases wrongly put and should be replaced by the question, "To what extent physical and to what extent psychic?"

The review relates to the possible importance of psyche in all the physical domains and from the standpoint of both clinical observation and experiment. Only a few examples must suffice as illustrations.

Under the general heading of Musculature, "Rheumatic Diseases" are considered. Mohr wrote in 1925, "Observations made during the War provided ample evidence of the extent to which the so-called rheumatic diseases are increased or 'fixated' by psychic factors. Of 100 cases that I carefully examined, 90, in which the illness had been of considerable duration, were cured by purely psychic treatment. Here as probably in cases of sciatica we must recognize the vicious circle: Pain, initially somatically conditioned, results in abnormal posture and muscle spasm; these are wrongly evaluated psychically, leading to increase of pains and again to abnormal posture, etc." J. Levy notes that muscular or articular rheumatism is one of the most frequent diagnoses to be met in the practice of socialized medicine; in countries with social insurance the percentage of these cases outnumbers the percentage of tuberculosis cases. He says that rheumatism has been proved to exist as a functional disease without primary organic alteration or, as we say today, as a neurosis of the motor organs. He points to the eminently practical value of such a conception and to the necessity of psychotherapy. Obviously here the term 'rheumatism' is used in a very broad sense and probably includes some of those cases often spoken of as muscular rheumatism, myositis, or fibrositis.

In introducing the chapter on "Endocrines" Dunbar states, "The endocrines, it has been said, translate the tempo of the nervous system into the tempo of metabolism and vice versa. They are therefore important

factors in the maintenance of equilibrium of organism in environment, and it is thus inevitable that those interested in the question of psychosomatic inter-relationships should find this field particularly inviting." In regard to the thyroid the syndrome of hyperthyroidism has been called the prototype of a nervous polyglandular disorder. The relationships of the glandular disorder and of the sympathetic nervous system naturally are stressed. The more extreme view of this disease would be as follows: The cause is an emotional disturbance that in a person with a peculiar constitutional predisposition operates through the thyroid gland and through the vegetative system in general to produce disturbances in many of the organ systems. There is produced, for example, in the heart, tachycardia, auricular fibrillation, cardiac dilatation, and cardiac failure: in the gastrointestinal system various functional disturbances; in the field of metabolism a marked increase in general metabolism, an elevation of the basal metabolic rate, loss of weight, emaciation, and perhaps a rarefaction of bones. The standard methods of treatment are not causal but symptomatic. The thyroid gland is treated by iodine medication and by sub-total thyroidectomy, thus interrupting the mechanism of the disease. For causal therapy the emotional disturbance must be discovered and treated. This may be superficial and easily disclosed, or it may lie at a deeper and less accessible level of the psyche.

In the chapter on the respiratory system the reviewer states that inasmuch as bronchial asthma is a controversial subject of considerable interest, the literature, as it pertains to the psycho-somatic problem, is reviewed in some detail. It is recognized that the modern literature concerning asthma is dominated by the concept of asthma as an allergic disease. Opinions as to the relative importance of psychic phenomena vary widely. Hansen writes, "In going over the English discussion of this subject (or the German, which is equally prone to extreme conclusions) one finds that points of view which apparently represent opposite poles can be maintained tenaciously only because neither side has sufficient experience to evaluate critically the arguments adduced by the other." There are numerous reports of successful psychotherapy; for example, Moos, a German internist, reports that in addition to milder cases he treated by intensive psychotherapy 16 asthmatics who were unable to work because of their disease. In all these cases the bronchitic lung signs disappeared at the end of the treatment. The emphysema subsided entirely or considerably except in two patients more than 50 years old. All cases ceased to have sputum and the Charcot-Leyden crystals and Curschmann's spirals disappeared also. The eosinophile cells in the sputum disappeared and the eosinophile count in the blood returned to normal. Exposure of these recovered patients to their supposedly important allergic factors did not result in a renewal of their attacks. Wittkower and Petow state that whether psychic factors play the rôle simply of one of many conditioning factors in the development of asthma, or whether asthma in a greater or lesser number of cases is to be

considered an organ-determined psychoneurosis, is a matter for discussion. The precipitation of single attacks by psychic influence in already established asthma has been known for a long time, since Hippocrates, and is not difficult to explain. The affect is discharged over the vegetative nervous system and mobilizes the mechanism already established, but the beginning of the asthma also is frequently preceded by violent psychic excitement. Emotions undoubtedly play a considerable rôle in the persistence of asthma. Since, however, many individuals live through violent emotional experiences without becoming neurotic or developing asthmatic attacks they cannot conceive of a purely affect-dynamic causation of neuroses or asthma. It is necessary to assume that the precipitating affect finds a psychic and probably also a somatic preparedness. They were interested in the relations between psychic and allergic mechanisms. It was found that although the patient's symptoms could be definitely affected by psychotherapy, a demonstrable allergic skin reaction could not be produced by hypnotic suggestion nor could an allergic skin reaction be eliminated by suggestion. Their concept of the psychogenesis of asthma was summarized as follows: (1) An allergic genesis of asthma without a neurotic component is certainly valid in many cases. (2) A pure psychogenesis without somatic predisposition is possible in itself, in many cases even probable, but unproved. (3) The vast majority of cases are doubly determined, whether it be that psychic factors in the presence of an allergic predisposition mobilize the latent tendency to illness, or whether it be that an allergic asthma becomes established secondarily in a neurotic superstructure.

In stressing the importance of affective disorders many other illustrations might be chosen from the studies on psycho-somatic relationships in reference to all the organ systems. The internist reviewing this literature already so helpfully prepared by Dunbar will, I feel sure, be surprised at the extent of these studies and perhaps shocked by some of the extreme views presented. Just how closely or how far away we follow these suggestions is just now, I think, not so very important. It is important that we consider them, that we give them a careful hearing or reading. A closer association with conservative psychiatrists may be helpful both to us and to our patients. We should at least be willing to admit that emotions can and frequently do cause changes in bodily functions, and be willing, when studying an ill patient, to follow Bleuler and ask the question, "To what extent physical and to what extent psychic?"

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STUDIES ON THE LIFE HISTORIES OF PATIENTS WITH CHRONIC ULCERATIVE COLITIS (THROMBO-ULCERATIVE COLITIS), WITH SOME SUGGESTIONS FOR TREATMENT *

By J. Arnold Bargen, M.D., F.A.C.P., Raymond J. Jackman, M.D., and Jack G. Kerr, M.D., *Rochester, Minnesota*

Two types of colitis in which intestinal ulceration occurs have long been recognized as entities; that is, tuberculous colitis and amebiasis. Until 1924, all other types of colitis were unconditionally assigned to the category of idiopathic or nonspecific colitis. There was a time after this when some felt that all cases denominated "idiopathic" or "nonspecific" were of streptococcal origin. It was thought that when the specific streptococcus was not isolated, the cause lay largely in the shortcomings of bacteriologic technic. As time went on, however, it became increasingly apparent that not all the cases laboring under the undescriptive term "chronic ulcerative colitis" were of one type. In the light of accumulated knowledge, reclassification of individuals who had ulcerative colitis seemed urgent. As the necessity of this became more and more apparent, we were faced with the question of where and when to start such a classification. Those of us who were especially interested in the lower segments of the gastrointestinal tract decided, on January 1, 1936, that thereafter we would divide all cases formerly laboring under the designation "chronic ulcerative colitis of nontuberculous and nonamebic origin," into three groups; that is, group 1, group 2 and group 3. In group 1 we placed those patients who presented the typical clinical, proctoscopic and roentgenologic picture encountered in chronic ulcerative colitis of the streptococcal variety. In group 3 we placed those who presented an atypical proctoscopic and roentgenologic picture and in group 2, those who did not give proctoscopic evidence of ulcerative disease of the rectum but who did give roentgenologic evidence of such disease. This separation into groups was made only for the sake of convenience and in the hope that something further might be learned about the etiology of groups 2 and 3, as well as for the purpose of trying to establish more adequate therapy.

Two years of this arbitrary classification prompted a review of a series of cases which came under our care after establishment of the importance of the streptococcus as an inciting factor in some of these cases. We felt that the establishment of a pattern of the life history of patients with chronic ulcerative colitis of the streptococcal variety might serve as a guide in our future classification and treatment of this intractable disease. Consequently

* Read before the meeting of the American College of Physicians, New York, N. Y., April 8, 1938.

we began our studies with the year 1925. In the years 1925 to 1931 inclusive the histories of 1000 of the patients registered at the clinic were filed under the heading, "chronic ulcerative colitis." In the same period, 73 patients who had tuberculous ulcerative colitis were studied and approximately 500 patients who had amebiasis, or infection with *Endamoeba histolytica,* were encountered. During these same years, many more cases in which the diagnosis was "mucous colitis" or "irritable bowel" were observed. Parenthetically, it may be said here that our present knowledge of function and disease of the intestine makes the term "mucous colitis" no longer tenable.

Recently the methods of following up patients by the medical profession have been challenged and this challenge served as a further stimulus to a very detailed statistical study and follow-up of these cases. Careful analysis of the 1000 records revealed that only 871 of the patients belonged in group 1; that is, in the group which presented typical clinical, proctoscopic, and roentgenologic features. The other 129 were of groups 2 and 3. It is our conviction that it is cases of the type of these 129 that have confused our knowledge of the etiology of bacterial ulcerative colitis. If the term "idiopathic" is to be used at all, it should be applied to the cases belonging to the groups to which this 129 belong. However, to encourage more intensive study of these and to discourage their glib acceptance as idiopathic or nonspecific, the term should be replaced by the designation "of unknown etiology." Buie and one of us (Bargen) have studied the inception, bacteriology, and pathology of chronic ulcerative colitis of the streptococcal type and feel that the term "thrombo-ulcerative colitis" can be suitably applied to this group of cases.

We have then tuberculous, amebic, and thrombo-ulcerative colitis, and ulcerative colitis of unknown etiology. This review is concerned specifically with the 871 patients who presented typical clinical, proctoscopic and roentgenologic evidence of a disease of bacterial etiology. The 871 cases will, henceforth in this presentation, be designated as cases of "thrombo-ulcerative colitis." Our study brought out the fact that the course and prognosis of this disease varied both as regards age of the individual afflicted as well, in many instances, as sex. Four hundred and ninety-one were males and 380 were females. Some of the tables that accompany this paper contain material which is not immediately called for by the relevant text, but since inclusion of such material does not obscure the points brought out, and since it is believed to add to the value of the report as a whole, it is supplied.

The native habitat of these patients is of some interest. Most of the states of the Union, except a few of the Southern states, were represented; for example, no patients in this series came from Florida, Georgia, the Carolinas, or Arizona. In nearly every instance, except Minnesota, the percentage of patients from the various states who had colitis, was greater than the percentage of patients of the clinic as a whole who came from these

states. In recent years 32 per cent of The Mayo Clinic patients have come from Minnesota. Only 12 per cent of the patients who had colitis came from Minnesota. On the other hand, 12 per cent came from Iowa, 12 per cent from Illinois, 7 per cent from Wisconsin, 5.5 per cent from New York, and 8 per cent from the various provinces of Canada, whereas registration at the clinic from these regions is 9, 9, 6, 0.8 and 5 per cent respectively. The rest of the patients come from widely separated regions of the United States and other countries, a few from Mexico, Panama, Puerto Rico, Peru and the South Sea Islands.

In many cases definite factors predisposing to the disease could be elicited (table 1). It will be seen from this table that such factors could definitely

TABLE I

Predisposing Factors in the Development of Thrombo-Ulcerative Colitis, Patients

Factor	Age at onset, years								Total
	Males				Females				
	0–9	10–19	20–29	30–74	0–9	10–19	20–29	30–74	
Upper respiratory infection	3	16	20	26	2	13	15	13	108
Childhood diseases	3	—	1	—	2	1	—	1	8
Dietary indiscretion	1	2	4	11	—	1	3	2	24
Physical and mental fatigue	—	4	6	6	—	2	5	6	29
Rectal surgery	—	—	4	6	—	2	2	3	17
Abdominal surgery	—	—	1	2	—	2	1	5	11
Trauma	1	1	1	2	—	1	—	—	6
Drastic catharsis	—	—	3	3	—	2	3	5	16
Foci with sepsis	—	1	3	1	—	2	3	3	13
Exposure	—	1	17	4	—	3	7	6	38
Dysentery epidemics	1	1	—	1	—	—	2	2	7
Pregnancy	—	—	—	—	—	3	17	7	27
Undetermined	10	49	109	167	9	35	89	99	567
Total	19	74	169	229	13	67	147	153	871

be elicited in 304 instances. Upper respiratory infections included tonsillitis, pneumonia, influenza, and otitis media. Foci of infection, with sepsis, were represented by mastoiditis, neisserian infection, and incomplete abortion. Pregnancy included those which went to term as well as those which were terminated by induced or spontaneous miscarriages. "Physical and mental fatigue" refers to unusual worry, the shock of a death in the family, and symptoms of menopause. It will be noted that the condition followed epidemic dysentery in only seven instances. The factors influencing relapse of the disease, once controlled, closely parallel those associated with the first attack (table 2).

It has been thought by some that this disease always begins in an insidious manner and that those cases which start with severe, or even ful-

TABLE II

Factors Influencing Relapses in Thrombo-Ulcerative Colitis, Patients

Factor	Age at Onset, Years								Total
	Males				Females				
	0–9	10–19	20–29	30–74	0–9	10–19	20–29	30–74	
Upper respiratory infections	5	16	25	39	1	16	15	17	134
Childhood diseases	—	1	—	—	3	—	—	—	4
Dietary indiscretion	—	—	5	—	—	—	2	3	10
Physical and mental fatigue	1	4	3	—	—	7	8	3	26
Foci with sepsis	—	2	14	8	—	3	6	3	36
Dysentery epidemics	—	1	—	—	—	1	—	—	2
Pregnancy	—	—	—	—	—	1	6	1	8
Indeterminate infection	1	—	—	—	—	—	—	—	1
Undetermined	12	50	122	182	9	39	110	126	650
Total	19	74	169	229	13	67	147	153	871

minating, bloody, purulent dysentery are not instances of the same condition. For convenience, we divided the cases into three types on the basis of early symptoms. In those cases in which the illness began with passage of one or more bloody, rectal discharges, without other apparent symptoms, the onset was said to be " insidious." If the condition began with sudden, severe, bloody dysentery but otherwise without symptoms of sepsis and toxemia, the onset was said to be " severe." If violent, bloody, purulent dysentery, with septic type of fever, great toxemia and rapid depletion were the elements of the initial episode, the onset was said to be fulminating (table 3).

TABLE III

The Character of the Onset of Symptoms in Thrombo-Ulcerative Colitis, Patients

Age at Onset, Years	Males				Females			
	Insidious	Severe	Fulminating	Total	Insidious	Severe	Fulminating	Total
0–9	7	9	3	19	5	5	3	13
10–19	34	33	17	84	25	28	14	67
20–29	84	52	33	169	83	40	24	147
30–74	117	73	39	219	89	34	30	153
Total	242	157	92	491	202	107	71	380

The manner of progression of this disease was carefully studied and its clinical course could readily be classified into eight types (table 4). Types 7 and 8 deserve particular comment. The illness of 41 males and of 11 females remained mild for months or years and then suddenly changed to

TABLE IV

The Manner of Progression of Thrombo-Ulcerative Colitis, Patients

Manner of Progression	Age at Onset, Years									
	Males					Females				
	0–9	10–19	20–29	30–74	Total	0–9	10–19	20–29	30–74	Total
1. Mild throughout entire course	—	10	28	48	86	2	4	31	34	71
2. Intermittent with declining severity	4	21	23	41	89	2	6	13	29	50
3. Septic course with complete recovery	—	2	11	10	23	1	7	9	4	21
4. Constant without remission	—	4	7	11	22	—	9	18	20	47
5. Slowly progressive without remission	4	7	32	46	89	4	6	24	20	54
6. Intermittent with progressive severity	7	17	55	49	128	1	30	47	40	118
7. Insidious onset with slow progression, changing to fulminating course and ending fatally	*4	11	8	18	41	3	2	5	1	11
8. Fulminating course throughout, ending fatally	—	2	5	6	13	—	3	—	5	8

a progressive, fulminating affair which ended fatally in spite of all therapeutic attempts, medical or surgical. That of 13 males and 8 females began as a violent fulminating disorder and progressed rapidly to fatality.

In a previous study [2] of the cause of relapses of thrombo-ulcerative colitis, the fact was brought out that relapses occurred more commonly during the months when upper respiratory infections were particularly prevalent than during other months. Hence, an effort was made to determine the month of onset of the symptoms. Only positive data were recorded. One might be inclined to deduce from this that June and October were the least likely months for invasion by this disease (table 5). Our clinical impression would thus be substantiated but we feel that larger series of cases should be accurately followed before such a deduction were drawn. This feature is being carefully observed in current cases. In this series of cases, positive data were at hand in only 627.

In several previous series of cases of ulcerative colitis, complications of these conditions were studied.[1] This is the first series of this size in which the study was limited strictly to thrombo-ulcerative colitis. It will be noted that 42 per cent of the males and 40 per cent of the females had complications of one form or another (table 6). It will also be seen that 20 per cent of the complications of males, but only 11 per cent of the complications of females, were multiple. This would tend to stress the observation that

TABLE V

Month of Onset of Thrombo-Ulcerative Colitis

Month	Patients		
	Males	Females	Total
January	36	16	52
February	29	16	45
March	22	14	36
April	23	9	32
May	20	16	36
June	15	10	25
July	22	18	40
August	22	15	37
September	23	14	37
October	14	11	25
November	23	12	35
December	19	16	35
Indeterminate	223	21	244

TABLE VI

Complications and Sequelae of Thrombo-Ulcerative Colitis among Children and Adults

Complication	Males			Females		
	Children	Adults	Total	Children	Adults	Total
Polyposis	48	42	90	7	44	51
Stricture	7	46	53	3	42	45
Perianal abscess-fistula	4	39	43	2	28	30
Arthritis	4	23	27	4	24	28
Erythema nodosum	1	4	5	—	4	4
Pyoderma gangrenosa	—	3	3	—	1	1
Perforation	1	6	7	—	3	3
Liver abscess	—	2	2	—	2	2
Carcinoma	5	14	19	1	8	9
Phlebitis	—	1	1	1	—	1
Iritis	—	3	3	—	2	2
Deafness	1	—	1	—	—	—
Splenomegaly	2	—	2	—	—	—
Nephritis	—	9	9	1	2	3
Psychosis	—	6	6	—	3	3
Massive hemorrhage	1	1	2	—	2	2
Endocarditis	1	3	4	—	5	5
Kidney stones	—	4	4	—	4	4
Multiple complications	10	80	90	7	35	42
Total individuals with complications	24	185	209	15	136	151

the disease may attack males more violently than it attacks females. Perhaps the reason for this may be found in the fact that the occupations of men lie more in the fields wherein upper respiratory infections and trauma are prevalent (tables 1 and 2).

The tendency for individuals who develop the conditions which we have called complications is for them to have more than one. Actually several

individuals have been known to have six or more of these. The unusually high incidence of carcinoma occurring in the course of this disease is worthy of mention. Every one of these patients was observed for years before carcinoma developed. In each instance, it was ushered in by a noteworthy change in symptoms. The carcinomas had a tendency to be multiple. In six instances, the patients were children whose disease began before the age of 10 years; five of these were boys. Death in these cases occurred between the ages of 15 and 25 years, and the downward course after first symptoms of carcinoma appeared was exceedingly rapid and in no instance lasted more than a few months. The incidence of carcinoma in the total group was 3.2 per cent. The incidence of carcinoma of the intestine as a factor in mortality, according to the United States Department of Commerce for 1923 to 1929 inclusive was 0.011 per cent. The incidence of carcinoma of the large intestine among patients of the clinic during these years was 0.88 per cent. These observations would point to one direction that the search for the cause of carcinoma might take.

Another point of particular note in table 6 is the fact that only four patients had liver abscess. When one thinks of the vascular drainage of the intestine, this becomes the more striking. It is also striking in its contrast to the cases of amebiasis, wherein liver abscess is the most common complication. A point of interest in this regard is the fact that in eleven of these cases, in seven of which the patients were men and in four of which they were women, a duodenal ulcer occurred in association with the thromboulcerative colitis.

A fair index of the severity of this disease in any given case can be obtained by study of the extent of the damage that has been inflicted on the bowel. This is best done by roentgenologic study, through retrograde filling of the colon with an opaque substance, and by the double-contrast method of examination. By these methods it was learned that in the majority of these 871 cases most of the large intestine became involved by the ulcerative process (tables 7 and 8). In 400 of the cases, 232 males and 168 females, the entire large intestine was involved when the patients were first examined. In 30 of these cases, 16 males and 14 females, the entire large intestine and terminal part of the ileum were affected. In 47 more cases the disease progressed between subsequent observations so that the entire large intestine became involved. In 558 cases (325 males and 233 females) only the one diagnostic roentgenologic examination of the large intestine was made. Although it is unwise to subject the intestines of these individuals to any avoidable trauma, yet in recent years it has been possible to make more observations per individual and hence the number of cases in which complete regression of the disease is known to have taken place has been greatly increased. Nevertheless, 16 males and 12 females of this group had lost all signs of the disease, as determined by proctoscopic and roentgenologic examination, at the time of subsequent observations. It is safe to assume that in many of the cases in which, in later tables (namely,

TABLE VII

Extent of Involvement of the Intestine by the Lesions of Thrombo-Ulcerative Colitis among Males, Demonstrated Roentgenologically

Age at Onset, Years	Total Patients	Extent of Involvement on Admission *					Single Observation	Subsequent Observations				
								No Change	Progression of Disease		Regression of Disease	
		1	2	3	4	4+			Slight	Marked	Slight	Complete
0–4	8	1	—	2	3	2	7	1	—	—	—	—
5–9	40	7	1	2	28	2	28	7	1	3	—	1
10–19	132	32	16	12	66	6	85	23	12	5	2	5
20–29	151	49	24	12	63	3	106	24	10	6	2	3
30–74	160	66	28	4	56	3	99	32	10	7	4	7
Total	491	155	69	32	216	16	325	87	33	21	8	16

* Involvement from rectum to sigmoid, 1; from rectum to splenic flexure, 2; from rectum to hepatic flexure, 3; entire colon, 4 and entire colon and terminal ileum, 4+.

TABLE VIII

Extent of Involvement of the Intestine by the Lesions of Thrombo-Ulcerative Colitis among Females, Demonstrated Roentgenologically

Age at Onset, Years	Total Patients	Extent of Involvement on Admission *					Single Observation	Subsequent Observations				
								No Change	Progression of Disease		Regression of Disease	
		1	2	3	4	4+			Slight	Marked	Slight	Complete
0–4	4	—	—	—	3	1	2	2	—	—	—	—
5–9	28	3	1	4	17	3	19	5	1	2	—	1
10–19	127	35	16	11	60	5	81	31	5	5	4	1
20–29	124	50	17	12	42	3	70	24	12	10	3	5
30–74	97	36	16	11	32	2	61	17	3	9	2	5
Total	380	124	50	38	154	14	233	79	21	26	9	12

* Involvement from rectum to sigmoid, 1; from rectum to splenic flexure, 2; from rectum to hepatic flexure, 3; entire colon, 4 and entire colon and terminal ileum, 4+.

tables 12 and 13) the patients are referred to as symptom-free, the same happy state of affairs is present, for represented among these are many patients free from all symptoms or signs of the disease for from 7 to 14 years. Tables 7 and 8 serve to give a broad view of the method of progression of this disease as observed roentgenologically.

There is no more impressive manner of emphasizing the serious nature of this disease than by study of tables of mortality. This is a study of the

life histories of patients who had thrombo-ulcerative colitis; hence, the immediate as well as the later mortality is discussed. All the deaths which occurred in the period of 14 years were considered. Among the patients treated medically, 284 males and 211 females, 81 had died before March 1, 1938. Of these, 13 had died from causes unrelated to the intestinal disease; the causes of their deaths, with the exception of one from suicide, were largely those generally associated with changes of old age; that is, apoplexy and other forms of vascular change. Twenty-eight died of conditions in which the major causes of death were not ulcerative colitis, but its presence was, more than likely, contributory (table 9). Forty died of the disease

TABLE IX

Mortality among Patients Treated Medically

Cause of Death	Males			Females		
	Children	Adults	Total Deaths	Children	Adults	Total Deaths
Carcinoma of rectum	1	1	2	—	—	—
Nephritis	1	1	2	—	2	2
Pneumonia	—	2	2	—	2	2
Hemorrhage	—	2	2	—	1	1
Lung abscess	—	1	1	—	—	—
Liver abscess	—	2	2	—	—	—
Perforation of colon	—	5	5	—	1	1
Inanition	—	3	3	—	1	1
Thrombo-ulcerative colitis and exophthalmic goiter	—	—	—	—	1	1
Thrombo-ulcerative colitis and large perirectal abscess	—	—	—	—	1	1
Thrombo-ulcerative colitis	7	28	35	—	5	5
Death unrelated to colonic disease	—	9	9	—	4	4
Total	9	54	63	—	18	18

without other complicating cause. The mortality among patients who were subjected to operation is reviewed in table 10. Among the 871 patients, 175 underwent some form of abdominal surgical intervention for attempted relief of the colitis, its complications, or other unrelated abdominal pathologic conditions. Seventy patients were operated on at the clinic. The multiplicity of surgical maneuvers is indicated in table 10. One individual underwent the following operations: cecostomy, colostomy three times, closure of the colonic stoma three times and ileostomy. Several individuals underwent ileostomy and ileosigmoidostomy at different times, or ileosigmoidostomy followed by ileostomy. Forty-two of the patients had been subjected to appendicostomy, cecostomy, or colostomy before their first examination at the clinic. Our study would suggest that appendicostomy and cecostomy fall far short of their desired effect. In this series of cases they rarely relieved, and never resulted in abatement of, intestinal symptoms.

Patients who had undergone a total of 125 surgical procedures were living March 1, 1938; of these, 27 patients stated that they were well; the intestinal symptoms of all the others have continued.

The causes of death are given in table 11. This portion of our study

TABLE X

Mortality among Patients Treated Surgically

Procedure	Operations *			Outcome			
				Living		Dead †	
	Total	Adult	Children	No.	Per cent	No.	Per cent
Appendicectomy	10	7	3	10	100	—	
Appendicostomy, cecostomy, colostomy	49	47	2	41	83	8	17
Ileostomy	98	86	12	60	62	38	38
Colectomy	10	10	—	7	70	3	30
Ileocolostomy	12	11	1	4	33	8	67
Closure of ileac stoma	1	1	—	—		1	100
Resection for carcinoma	1	1	—	—		1	100
Other abdominal surgery	11	9	2	3	27	8	73
Total	192	172	20	125	66	67	34

* Of these surgical procedures, 87 were performed at The Mayo Clinic and 105 elsewhere. Of the latter, 62 were carried out before the patient came to the clinic the first time. If one individual underwent more than a single operation, each operation was entered once; 175 individuals underwent the 192 operations listed. Ileocolostomy includes ileosigmoidostomy.

† Deaths include those which occurred in hospital. If a patient underwent several operations, death was listed against the last operative procedure.

TABLE XI

Causes of Death of Patients Treated Surgically: 106 Males and 69 Females

Cause of Death	Males			Females		
	Total Deaths	Children	Adults	Total Deaths	Children	Adults
Peritonitis	14	1	13	8	1	7
Embolism	2	—	2	—	—	—
Inanition	3	—	3	—	—	—
Pneumonia	1	—	1	—	—	—
Carcinoma	11	5	6	5	1	4
Obstruction	3	1	2	2	—	2
Multiple liver abscess	1	—	1	—	—	—
Addison's disease	—	—	—	1	—	1
Died elsewhere immediately after making of stoma	4	1	3	—	—	—
Died elsewhere later after making of stoma	5	1	4	7	—	7
Total	44	9	35	23	2	21

further emphasizes the very serious nature of this disease and suggests very strongly that surgery should be limited to complications.

The disease is particularly ravaging among children in the first decade of life and responds relatively poorly to present forms of treatment (tables 12 and 13). After the first decade of life, response to treatment is increasingly more favorable. The outlook among children who have suffered severely from this disease is rather gloomy. In general it can be said that the older the individual afflicted, the better the outlook for recovery.

TABLE XII

End Results of Treatment of 491 Male Patients with Thrombo-Ulcerative Colitis Observed for Seven to Fourteen Years

Age at Onset, Years	Total Number	Results											
		Symptom Free		Good		Satisfactory		Good Progress, Per cent of Cases	Unsatisfactory		Dead at Time of Inquiry		
											Total		Cancer
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	Number	Per cent
0–9	19	5	26.3	4	21.0	3	15.8	64	7	36.8	6	31.6	5	26.3
10–19	74	28	37.8	15	20.3	10	13.5	72	21	28.4	14	18.9	4	5.4
20–29	169	69	40.8	32	18.9	34	20.1	78	34	20.1	26	15.4	2	1.2
30–74	229	98	42.8	34	14.8	32	14.0	76	65	28.4	49	21.4	3	1.3
Total	491	200	40.7	85	17.3	79	16.1		127	25.9	95	19.3	14	2.8

TABLE XIII

End Results of Treatment of 380 Female Patients with Thrombo-Ulcerative Colitis Observed for Seven to Fourteen Years

Age at Onset, Years	Total Number	Results											
		Symptom Free		Good		Satisfactory		Good Progress, Per cent of Cases	Unsatisfactory		Dead at Time of Inquiry		
											Total		Cancer
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	Number	Per cent
0–9	13	3	23.1	4	30.8	2	15.4	69	4	30.8	3	23.1	1	7.7
10–19	67	20	29.8	9	13.4	14	20.9	64	24	35.8	11	16.4	—	—
20–29	147	63	42.8	19	12.9	29	19.7	76	36	24.5	15	10.2	3	2.0
30–74	153	60	39.2	34	22.2	22	14.4	76	37	24.2	20	13.1	6	3.9
Total	380	146	38.4	66	17.4	67	17.6		101	26.6	49	12.9	10	2.6

The principles of treatment worked out for each of these different types of ulcerative colitis have been fairly well standardized.

In the cases of amebiasis or amebic colitis, chemotherapy plays the major rôle. The effort is to eradicate the *Endamoeba histolytica* and promote healing of the diseased bowel. The drugs in common use have been principally three: ipecac and its derivative, emetine hydrochloride; arsenic in the form of stovarsol, the methenamine derivative of meta-amino-para-oxyphenylarsenic acid (treparsol), or carbarsone, and complex products of iodine, that is, vioform, iodoxy-quinoline sulphonic acid (anayodin), chiniofon, and the like. Promotion of intestinal rest is indicated in all types of ulcerative colitis.

Whenever the diagnosis of tuberculous colitis is established, the place for the patient is a sanatorium or a similar place devised for the care of the tuberculous.

A well-ordered program for the care of the patient with thrombo-ulcerative colitis includes the administration of serums and vaccines directed against the offending streptococcus, a diet rich in calories, high in proteins, and low in residue, frequently a series of transfusions of small amounts of blood (200 to 250 c.c. at a time), removal of foci of infection, good nursing care, adequate rest of the bowel and other symptomatic measures. Chemotherapy has a very small place in the management of this disease. Innumerable drugs have been used in the hope that some "quick cure" might be found. We shall mention only a few that have been tried and found wanting. Calcium and parathyroid extract had their day; their usefulness is negligible in this condition. Arsenic does great harm in many of these cases. Azochloramid has had its advocates recently. As a local application, it causes much intestinal irritation. Kaolin and aluminum hydroxide for rectal instillation serve only to soothe the rectum in some of the milder cases. Histidine hydrochloride apparently has a small field of usefulness in a few cases. The recent furor about sulfanilamide and allied drugs naturally led to its trial in cases of this infection. Results with it can be summarized about as follows: In a few of the milder cases, with involvement of distal segments of the bowel alone, striking improvement has followed its administration.[4] In most of them no apparent effect was achieved. In any event, these are not the cases wherein help is greatly needed. Progress in these cases, under the program mentioned above, is satisfactory. It is in the severe cases of fulminating disease that we are groping for help. In them, the sulfanilamide group of drugs so far has not proved of value, because the margin between safety and toxicity is not great. In four cases in which patients who had received these drugs came under our observation, hepatitis with jaundice was encountered; in three cases the patient died and in another one peripheral neuritis developed.

Many medicines have been tried in an attempt to control this disease. So far no single drug has offered much help for more than a few patients. Many have been misled by the apparent brilliant results achieved by single

therapeutic agents in a few cases. Careful analysis of these results invariably has revealed that the cases were mild and that involvement was only of distal segments of intestine. Probably the most important factor in the treatment of these cases was rest.

Solution of the whole therapeutic problem depends on better understanding of this infection. Let it be remembered that the infection is destructive, progressing, in many respects similar to tuberculosis, and therefore let a program of management for its control be adopted; search for a " miraculous cure " should not be continued. The keynote of the program should be the attempt to reverse a devastating and destructive infection. The patient must adopt the philosophy of life that the patient with peptic ulcer is supposed to have.

Quite a different situation exists in the group of 129 cases of unknown etiology. Some of these cases are, more than likely, of the nature of the end results of a state of deficiency. Vitamin concentrates and vitamin therapy in general have afforded striking relief in some of them. Here trial of the various therapeutic aids advocated from time to time seems justified.

Summary

During the years 1925 to 1931 inclusive, 73 patients who had tuberculous ileocolitis, approximately 500 who had amebic colitis, 129 who had ulcerative colitis of undetermined etiology, and 871 who had thrombo-ulcerative colitis were observed at The Mayo Clinic. A chiefly statistical study was made of the records of the 871 patients who had thrombo-ulcerative colitis. It tells the story of patients who have been followed from 7 to 14 years after first observation. All ages recorded in the paper concern the age of onset of symptoms of the disease.

Predisposing factors and factors affecting relapses of the disease are chiefly the following: upper respiratory infection, disease of childhood, dietary indiscretion, physical and mental fatigue, rectal or abdominal surgical operation, trauma, drastic catharsis, foci of infection with sepsis, exposure, dysentery epidemics, and pregnancy.

This disease may begin in an insidious manner. Again, it may come on suddenly, as a violent diarrhea without toxic symptoms, or it may start in a fulminating fashion, associated with marked toxemia, fever and all the concomitants of a severe septic process.

On the basis of its course, the disease can be readily divided into the following types: (1) mild throughout, (2) intermittent with declining severity, (3) septic with complete recovery, (4) constant without remission, (5) slowly progressive without remission, (6) intermittent with progressive severity, (7) insidious onset with slow progression, changing to a fulminating condition and ending fatally and (8) fulminating throughout, ending fatally.

The major complications and sequelae of thrombo-ulcerative colitis include polyposis, stricture, perianal abscess-fistula, arthritis, erythema nodosum, pyoderma gangrenosa, perforation, liver abscess, carcinoma, phlebitis, iritis, deafness, splenomegaly, nephritis, psychosis, massive hemorrhage, endocarditis and kidney stones.

There is no special time of year in which this disease begins but it is of interest to note that more of the cases had their onset in January, February, or July than in the other months of the year.

The progress of the invasion from the rectum toward the cecum is indicative of the destructive nature of the disease. This is best observed by the roentgenologist. The mortality associated with this destructive infection emphasizes its serious nature.

Surgical intervention in this disease should be limited to complications and sequelae. Some of these demand wisely chosen surgical measures, both from the standpoint of the time of their application and from that of the lesion present. An individual afflicted with thrombo-ulcerative colitis presents a poor surgical risk if a surgical attempt must be made to relieve another intercurrent abdominal pathologic condition.

The end results of this infection may be devastating but it may also end in complete relief of all symptoms and signs of intestinal pathologic change. This happy result occurs frequently enough to make it urgent that a well-ordered regimen be followed without deviation by these patients for months and years.

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QUININE AND ATEBRINE—A COMPARISON *

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To be tremendously over-rated when first introduced is quite a characteristic event in the history of all new remedial agents—especially of specifics. Then after the pendulum has swung in the opposite direction through the condemnations of the ultra-conservatives a return towards a correct estimate of the remedial measure may be expected.

Practically ever since the historical occasion when a decoction from the bark of a Peruvian tree first effected a spectacular cure in the oft-cited case of Cinchona, the wife of the Spanish Viceroy to Perú, substitutes for this bark and its derivatives have been eagerly sought because of the many disagreeable features which attend a thorough treatment with cinchona and its alkaloids. Among the disadvantages are the lengthy periods of treatment which are necessary; the disagreeable bitterness of the drug; the tinnitus aureum; the general malaise produced by the drug alone; the reputed action on the pregnant uterus; the occasional deafness and amblyopia attending intensive treatment; the economic disadvantage of prolonged disability; and the serious anaphylactic-like complications which occasionally are noted when idiosyncrasies exist.

We who are particularly interested in tropical medicine were so often disappointed with the various substitutes for quinine which appeared on the market from time to time—especially such as stovarsol and that inglorious panacea namely intravenous mercurochrome—that plasmochin and atebrine were tried out with some reluctance at first by many investigators. The value of plasmochin as a gametocide soon, however, became appreciated; and many of us were most favorably impressed with its application as a sanitary measure in some of our United Fruit Company Divisions where it undoubtedly reduced our malarial index quite remarkably. As evidence of this I refer to the several annual reports of the Medical Department of the United Fruit Company from 1926 to 1931. Atebrine was brought out later; and in that its action was reported to be directed specifically against asexual forms only of the parasites, it appeared that it might possibly be used as a substitute for quinine, and accordingly be given successfully in conjunction with plasmochin. The important consideration then was to determine the comparative values of quinine and atebrine. I do not intend to review the results of the extensive investigations that have already been reported but it is worthy of mention that these indicate that in the last analysis some writers still prefer quinine while other enthusiasts extoll atebrine and welcome it eagerly as a substitute for the older therapeutic agent. Our in-

* Received for publication December 4, 1936.

vestigation in this hospital was purely of a practical nature and, due to lack of certain facilities, we did not attempt the type of research reported by Manson-Bahr and Walters in the *Lancet* of January 6, 1934, but rather groped along lines of study to determine which drug, in the main, might be more practical for our use in the various Divisions of our Company where often rather unusual conditions prevail.

The holdings of the Magdalena Fruit Company extend from the Port, namely Santa Marta, a city of some 25,000 inhabitants and incidentally the oldest town built by foreigners in the entire Western Hemisphere, inland some 70 miles to the farthest banana farms. This torrid littoral, which slopes from Andean heights of perennial snow towering over 19,000 feet, is so dry that the farm lands require irrigation during the months principally from December to April. The heaviest rainfall occurs usually during the months of October and November. In table 1 is the rainfall report which was kindly submitted by the Agricultural Department.

TABLE I

Average Division Rainfall in Inches

Year	1928	1929	1930	1931	1932	1933	1934	1935
January						.06	.18	
February			.01	.08				.72
March	.57	.80	.63	1.73	.10	.38		.07
April	.70	1.89	3.21	4.96	5.59	1.07	1.40	1.84
May	6.74	3.31	3.16	10.12	6.69	9.20	9.01	7.12
June	5.95	6.27	4.48	9.36	5.83	6.46	9.92	7.68
July	1.80	3.36	2.28	16.40	6.43	6.81	1.47	4.54
August	7.99	4.39	3.97	2.38	9.68	11.05	2.58	11.75
September	8.69	5.28	4.71	10.94	11.13	13.48	2.61	5.82
October	7.79	15.76	6.16	8.36	18.39	11.91	15.65	8.53
November	8.39	2.95	.50	9.40	13.61	17.50	5.82	
December	.03		.10	.80	.74	1.90	2.10	
Year	48.75	44.01	29.21	74.52	78.14	79.88	50.70	

(*Note:* 1928 and 1929 include Río Frío.)

The relation between rainfall and malarial infection during the various months can be determined by reference to the tabulations of hospital admissions (table 2).

Our medical staff consists of seven physicians, four of whom constitute the staff of the Santa Marta Hospital (an institution of about 100 beds at this time), the other three being stationed in various dispensaries in the farming districts. The milder cases of malaria are treated in the dispensaries while only the more serious cases, or cases where malaria is found as a secondary diagnosis during the routine physical and laboratory examinations, are treated in the hospital. When we arranged to attempt this investigation, it was decided that all cases which were admitted to the hospital with malaria as either a primary or secondary diagnosis, would be included in this series and that there would be absolutely no selection of cases for

either drug. Accordingly, the first 10 cases were treated with atebrine and the second 10 with quinine. Thus after each group of 10 cases the treatment was alternated until a series of 200 cases was completed, 100 with quinine and 100 with atebrine. Sixteen and one-half months were required to complete this series, that is from July 1, 1934 to November 15, 1935 when the last case of the series appeared. The distribution of these cases by months is shown in table 2.

Of these cases only six were below the age of 12 years; of the others, 169 were men and 25 women.

Some of the smears were reported as " rings and tertian." These were classed as tertian and not as mixed infections. It chanced that in the atebrine

TABLE II

	Estivo-Autumnal	Tertian	Quartan	Mixed	Total Cases
1934					
July	4	2	1	—	7
August	6	2	—	—	8
September	—	1	—	—	1
October	4	1	—	EA & Q 1	6
November	11	8	1	—	20
December	16	11	2	—	29
1935					
January	19	10	3	EA & Q 1	33
February	14	2	2	—	18
March	11	3	3	—	17
April	6	1	—	—	7
May	2	3	—	—	5
June	2	1	4	—	7
July	8	7	—	—	15
August	4	2	1	—	7
September	3	3	1	—	7
October to Nov. 15	8	3	—	—	11
	2	—	—	—	2
	120	60	18	2	200

series 63 were estivo-autumnal cases, 31 tertian and 6 quartan while the quinine group contained 57 estivo-autumnals, 29 tertians, 12 quartans and 2 mixed infections of quartan and estivo-autumnal.

In every case of each series, one plasmochin compound tablet was administered every night as this, in earlier research studies, was found to be quite sufficient for complete gametocidal effect.

In the discussion of dosage in this article, the tablet will be given as the unit in order to make better comparisons regarding the costs of the different drugs. The quinine tablet contained 5 grains or 0.33 gram; the atebrine tablet, 1.5 grains or 0.1 gram; and the plasmochin compound tablet containing quinine 0.125 grams, and plasmochin 0.01 gram.

In the series of 200 cases three resulted in death, in each of which malaria

was only a contributory cause; one, a Scotchman having been admitted to the hospital with lobar pneumonia, and the other two having succumbed to cardio-renal disease with broken compensation. Two of these, the lobar pneumonia case and one of the cardio-nephritics, happened to have belonged to the quinine group while the third received atebrine treatment for the co-existing malaria. The last named case had completed his atebrine course several weeks before his death, for which the drug therefore could hardly be held responsible. One patient of the atebrine series completed his course of therapy but was discharged by mistake before his blood and urine specimens were rechecked.

All atebrine cases were treated strictly in the orthodox manner, that is, three tablets were given each day (one three times a day) for five days. The urine was examined before treatment and again after the treatment was completed. Likewise on the sixth day a thick film was examined, and if asexual forms were found the atebrine course was repeated after a lapse of a few days.

The quinine cases were treated in our usual manner. Ten grains of quinine were administered three times a day until the fever had subsided and for at least five days thereafter or for five days after all symptoms, save those due directly to the quinine, had disappeared. Serious cases, such as the various pernicious types, were treated, of course, with a heavier dosage. Thus the quinine treatment required usually a considerably longer hospitalization period, but it seemed only fair to treat these cases exactly as we had always handled them before. Thus only could a reasonably fair comparison be drawn. In this series also the urine was tested before treatment, and both a urine specimen and a thick film were examined after completion of the course of treatment. If asexual forms were found the treatment was continued for five days longer. When sexual forms alone were found in either the atebrine or the quinine cases after the usual course of treatment, plasmochin compound tablets were given, one three times a day, until the blood smears became and remained negative. At least five minutes were devoted to each thick film examination. Upon final discharge the atebrine cases were given 24 special tonic tablets (Aitkins formula plus an extra grain of quinine in each tablet) to take home, recommending that they take one three times a day. The quinine series were given 24 special tonic and 24 quinine tablets, one of each to be taken three times a day.

The patients in both series were chiefly Colombian mestizos and mulattoes, of the laboring class, these numbering 190. Among the remaining were: White Americans 3, Spaniards 2, Scotch 1, Venezuelan mestizo 1, and West Indian negroes 3, one each from Jamaica, Martinique and Grenada.

Other conditions which had to be treated in the various cases along with the malaria, some times as primary, but more frequently as secondary ailments, are listed in table 3.

TABLE III

Associated Diseases

Unciniarisis	60
Ascariasis	31
Amebiasis and amebic dysentery	31
Lobar pneumonia	1
Bronchitis	1
Lung abscess	1
Influenza	9
Tuberculosis	1
Syphilis	14
Gonorrhea (ophthalmia and urethritis)	4
Chancroid	1
Inguinal adenitis	1
Obstetrical cases	3
Cystocele and rectocele with prolapse of uterus	1
Cervicitis	1
Mitral regurgitation	2
Cardio-renal case	2
Nephritis	1
Otitis media	1
Axillary abscess	1
Contusion	1
Stab wound	1
Infection of leg	1
Conjunctivitis	2
Dental caries	11
Splenic anemia	1
Psychasthenia	1

To reach conclusions from this study of 200 cases, 12 important features must be given consideration. These are as follows:

1. Comparative efficiencies of quinine and atebrine relative to their action on the asexual forms.
2. Do both drugs act equally well with plasmochin?
3. Comparative costs of the drugs.
4. Does atebrine appear to be more toxic to the human organism than quinine?
5. Is atebrine more pleasant to take than quinine?
6. Do patients seriously object to the yellowish pigmentation of the skin which is often produced by physiological doses of atebrine?
7. Is the slight gastric distress which attends atebrine ingestion more disagreeable than the tinnitus aureum produced by quinine?
8. Which cases seem more prone to relapse—those that have been treated by quinine, or the atebrine cases?
9. Which drug yields the better results in severe pernicious malaria such as the biliary remittent, the cerebral, the algid or the cardiac types where intramuscular or intravenous therapy only can be applied?
10. The effect of both drugs on the kidneys.
11. The economic aspect, as determined by observing which type of treatment returns patients to their various duties more promptly.
12. Consideration of the effects of atebrine and quinine on the pregnant uterus.

ATEBRINE SERIES

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Days 1	EA ####	EA #	EAc #	T #	EA & c #	EA #	EAC #	T #	T ###	EA ##	T ####	T ##	EA ##	EA ##	T ##	EA ####	T ###	EA ###	T ####	EA ##
2	EA & c #	— Neg.	EA & c #	T ##	EA & c #	— Neg.	EAc (#)	T #	T ###	EA (#)	T ###	— Neg.	— Neg.	EA #	T #	EAc ##	T ###	EA ###	T ####	EA ###
3	EA & c #	Neg.	EAc #	T #	Neg.	Neg.	Neg.	Neg.	T ##	EA & c #	T #	Neg.	Neg.	EAc ##	Neg.	EA & c ###	T #	EAc ##	T ###	EA (#)
4	EAc	Neg.	Neg.	T #	Neg.	Neg.	Neg.	Neg.	T #	EA & C #	Neg.	Neg.	Neg.	EAc ##	Neg.	EAc #	Neg.	EAc #	T ###	EAc #
5	EAc	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	EA & c (#)	Neg.	Neg.	Neg.	EAc ##	Neg.	EAc #	Neg.	EAc (#)	T ##	EAc #
6	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	EAc ##	Neg.	EAc #	Neg.	Neg.	T #	EAc (#)
7	Neg.	Dis.	Dis.	Neg.	Neg.	Dis.	Dis.	Dis.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	EAc #	Neg.	Neg.	Neg.	EAc (#)
8	Dis.			Dis.	Dis.				Dis.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Dis.	Neg.	Neg.	Neg.
9										Neg.	Dis.	Dis.	Dis.	EAc (#)	Dis.	Neg.		Neg.	Neg.	Neg.
10										Dis.				Neg.		Neg.		Dis.	Neg.	Neg.
11														Neg.		Dis.			Dis.	Dis.
12														Neg.						
13														Dis.						

QUININE SERIES

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Days 1	T	Qtn	Qtn	EA	EA	EA	EA	EA	EA	EA	T	EA	Qtn	Qtn	Qtn	T	EA	Qtn	EA	EA
	#	###	##	#	#	##	#	####	##	##	####	#	###	####	#	###	(#)	##	####	####
2	—	Qtn	Qtn	—	—	EAc	EA	EA	EA	EA	T	EA	Qtn	Qtn	—	T	—	Qtn	EA	EA
	Neg.	###	##	Neg.	Neg.	##	##	#	##	##	####	#	#	####	Neg.	###	Neg.	##	###	###
3	—	Qtn	Qtn	—	EA	EA	—		EA	EA	T	—	Qtn	Qtn	—	T	—	Qtn	EA	EA
	Neg.	##	#	Neg.	#	##	Neg.	EAc	#	##	#	Neg.	##	###	Neg.	##	Neg.	#	####	#
4	—	Qtn	Qtn	—	—	EA & c	EAc	—	—	EAc	T	—	Qtn	Qtn	—	T	—	Qtn	EA	—
	Neg.	##	#	Neg.	Neg.	##	#	Neg.	Neg.	##	#	Neg.	#	##	Neg.	#	Neg.	#	##	Neg.
5	—	Qtn	—	—	—	EA	—	—	—	EAc	—	—	Qtn	Qtn	—	—	—	Qtn	EAc	—
	Neg.	#	Neg.	Neg.	Neg.	#	Neg.	Neg.	Neg.	#	Neg.	Neg.	#	##	Neg.	Neg.	Neg.	#	##	Neg.
6	Neg.	Qtn	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	EAc	Neg.	Neg.	Neg.	Qtn	Neg.	Neg.	Neg.	Qtn	EAc	Neg.
		#								#				#				#	##	
7	Dis.	Neg.	Dis.	Dis.	Dis.	EA	Neg.	Neg.	Dis.	Neg.	Neg.	Dis.	Neg.	Qtn	Dis.	Neg.	Neg.	Neg.	EAc	Neg.
						##								##					#	
8		Neg.				EA	Dis.	Neg.		EAc	Dis.		Neg.	Neg.		Neg.	Neg.	Neg.	EAc	Neg.
						##				(#)									#	
9		Neg.				EA		Dis.		Neg.			Dis.	Qtn		Dis.	Dis.	Neg.	EAc	Dis.
						#								(#)					#	
10		Neg.				Neg.				Neg.				Neg.				Dis.	EAc	
																			(#)	
11		Dis.				Neg.				Neg.				Neg.					Neg.	
12						Neg.				Dis.				Neg.					Neg.	
13						Dis.								Dis.					Neg.	
14																			Dis.	

The discussion of these 12 considerations is as follows:

1. *Comparative Efficiency of Quinine and Atebrine, Relative to Their Actions on the Asexual Forms:* It is true that often the malarial parasites seem to leave the peripheral circulation when the patient is simply put to bed, given good food, rest, ample fluids to prevent dehydration, and alkalinization, even though no specific drugs are administered. It is also true that parasites may be found on thick film examination on a given day and be absent on the next even though the patient has not received even the above described attention. It is moreover true that change of climate, of altitude, exposure to cold, to roentgen-ray treatment, or any lowering of the individual's normal resistance may induce deep seated parasites to enter the peripheral circulation. Yet despite these considerations the best test for comparative efficiency seemed to lie in making daily examinations of thick films in sub-groups of unselected cases while under treatment with these drugs. Hence 20 cases were used in each sub-group, the results of which are shown on pages 359 and 360.

As regards the abbreviations in the above tabulation, E.A., of course, stands for estivo-autumnal; Qtn, for quartan; and T for tertian; c stands for crescents; EA signifies rings; and EA&c indicates the presence of rings and crescents. The sign ✻, used as a plus sign, indicates the degree of infection, (✻) meaning ½ plus or equivalent to occasional or extremely few. Dis. stands for discharge from hospital.

In almost every case at least three daily negatives were obtained before the case was discharged. These may be considered to mean permanently negative. In some of the cases longer series of negatives were required, chiefly because they were suffering from coexisting maladies and we wanted to be certain that such a sign as continued fever for example might not have been augmented in any way by the malaria. In the atebrine sub-group, contrary to our general plan, atebrine was continued without any lapse where ring forms still persisted on the fifth day. It chanced that the atebrine series contained 12 E.A., and 8 T., cases, while the quinine cases were represented by 11 E.A., 6 Qtn., and 3 T.

In concluding this, the first of the 12 features, we find that the blood films became permanently negative in an average of 4½ days in the atebrine sub-group and in the quinine sub-group not until 5⁷⁄₂₀ days. But consideration must be given to the fact that the atebrine series contained no quartan cases and that may make some difference. Relapses and length of hospitalization will be considered under separate headings.

2. *Do Both Drugs Act Equally Well with Plasmochin?* In our experience no incompatibility appears to exist between plasmochin and either quinine or atebrine, and each of the latter seem to act in perfect accord and therefore equally well with plasmochin.

3. *Comparative Costs of the Drug.* We find that delivered to us in Santa Marta, with duty, cost of shipment and all, the cost of quinine per

tablet is 0.0120 pesos, Colombian currency, atebrine 0.0425 pesos, plasmochin compound 0.02 pesos, and ampules of the di-hydrochloride of quinine for intravenous or intramuscular use, each of which contains 7½ grains or ½ gram, cost 0.08 pesos each. The American dollar at the present exchange is worth in Colombia approximately 1.75 pesos. Our investigation shows that in the treatment of 100 cases, 1,590 tablets of atebrine were used. The cost of these at 0.0425 pesos per tablet amounted to 67.575 pesos. In treating the quinine cases, as we did, giving each patient also 24 tablets to take at home with the special tonic tablets after his discharge, 7,160 tablets were used. At 0.012 pesos per tablet the cost of treating the series of 100 cases rose to 85.96 pesos. In addition to the tablets of quinine, 14 ampoules of the di-hydrochloride were also used for the treatment in certain of the pernicious manifestations. It chanced that in the atebrine series none of the cases required intramuscular or intravenous therapy. As our routine included the administration of one tablet of plasmochin compound every night, and as the quinine series required longer hospitalization, 549 plasmochin compound tablets were used in the atebrine series against 736 in the quinine group.

4. *Does Atebrine Appear to Be More Toxic to the Human Organism than Quinine?* No real objective signs of any toxicity were noted, and I do not believe that the yellowish pigmentation of the skin enters into this category. Urine examinations before and after treatments will be discussed under a separate heading. None of the cases in either group manifested idiosyncrasies. This was fortunate for when this phenomenon complicates quinine administration it can be not only extremely distressing but also quite alarming. We have as yet seen no such untoward manifestation with atebrine.

5. *Is Atebrine More Pleasant to Take Than Quinine?* Even though atebrine is bitter nearly all patients agree that it is more pleasant to take than is quinine. To children it can be given in required fractions of tablets while quinine has always to be prescribed either in the form of the comparatively tasteless and far less soluble ethyl carbonate, which is expensive, or must be disguised by syrup or other sweetened adjuvants. For adults, the bitterness of the quinine need cause scarcely any discomfort since sugar coated tablets are found to be quite as soluble as the uncoated ones.

6. *Do Patients Seriously Object to the Yellowish Pigmentation of the Skin Which Is Often Produced by Physiological Doses of Atebrine?* The few really white skinned patients in our series did not object; in the others, chiefly mulattoes and mestizos, it was scarcely noticeable.

7. *Is the Slight Gastric Distress Which Attends Atebrine Ingestion More Disagreeable than the Tinnitus Aureum Produced by Quinine?* In this the opinions of patients who had taken both drugs were equally divided, the more phlegmatic apparently not objecting as much to the tinnitus as to the gastric discomfort when the latter was in evidence. In most cases no gastric symptoms were noted. I do believe that in field work and for blanket treat-

ments, the average patient would be more likely to take the course of 15 atebrine tablets than a course of quinine which would require at least double or triple that number of tablets.

8. *Which Cases Are More Prone to Relapse—Those That Have Been Treated by Quinine, or the Atebrine Cases?* In each series 5 cases were known to relapse or become re-infected. In the atebrine series there were 3 tertians and 2 estivo-autumnal cases which, when they were readmitted to the hospital, were found to have tertian parasites. One of the tertian cases was readmitted twice, each time at several months intervals. The quinine relapse group presented 3 estivo-autumnals and 2 tertians one of which, on returning, was found to have estivo-autumnal organisms. Other cases might have relapsed and returned for dispensary treatment only. We would have no record of these.

9. *Which Drug Yields the Better Result in Severe Pernicious Malaria Such as the Biliary Remittent, the Cerebral, the Algid or the Cardiac Types Where Intramuscular or Intravenous Therapy Only Can Be Applied?* We have in our possession ampules of atebrine for intramuscular and intravenous use. It chanced that the atebrine series presented no pernicious case which required extra-oral administration of the specific, and we were determined, when we began this investigation, that we would not select cases. Frankly, I have had such satisfactory results generally with the intramuscular injections of quinine combined with adrenalin, or by giving quinine intravenously, very slowly and cautiously, well diluted in saline (or preferably hypertonic glucose solution), that had I had, for example, in my atebrine series a case either unconscious with cerebral malaria or with such persistent vomiting as to preclude oral administration of the drug, the sort of complication one finds in the biliary remittent type (incidentally the commonest and fortunately the least dangerous of the pernicious forms), I should unhesitatingly have used this form of quinine treatment first, to be followed, when possible, by atebrine by mouth. And this is the type of treatment I now unhesitatingly advise until we learn more about the intravenous and intramuscular administration of atebrine.

10. *Effect of Both Drugs on the Kidneys.* Traces, and even larger amounts of albumin, and hyaline and occasional granular or even epithelial casts are signs of the cloudy swelling of the kidneys which, along with all the other parenchymatous organs, are involved in any such febrile condition as malaria. It is not surprising then that our records show substantial improvement in the urinary picture in the majority of specimens examined after the treatment had been completed. This is illustrated in the following tabulation:

	Atebrine	*Quinine*
Substantial improvement after treatment	49	51
Condition about the same after treatment	9	7
Condition worse after treatment	5	3
Urine picture normal both before and after treatments	36	36
No second specimens obtained	1	3

Some of the cases, of course, as herein before stated, suffered primarily from kidney conditions while in other instances renal degeneration continued to progress because of aggravation from the various contributory diseases mentioned in the foregoing list of secondary ailments.

11. *The Economic Aspect, by Determining Which Type of Cases Return to Their Various Duties More Promptly.* I have stated before that the atebrine course of therapy is generally definitely shorter than the quinine course. Counting the hospital days from the temperature charts would not be absolutely correct because it was necessary frequently to retain patients for treatments of conditions other than malaria. As accurate a way as any to make an estimate from our investigation would be to double the 1,590 atebrine tablets used in the series because of these only 3 were used each day, and determine the ratio between that sum and the amount represented by the 7,160 quinine tablets from which 2,400 should be deducted in that this amount was given to the patients to take home with them. Thus the ratio of the average atebrine hospitalization time to the average hospitalization time for quinine cases is as 3,180 is to 4,760, signifying that atebrine cases are kept in the hospital for treatment only about two-thirds as long as the quinine cases.

12. *Consideration of the Effects of Atebrine and Quinine on the Pregnant Uterus.* One case, a young American primipara, was given a complete course of atebrine and plasmochin compound almost at the end of her confinement. It produced absolutely no untoward effect, and influenced in no way whatsoever a quite normal delivery at full term.

Despite the insistence of some of our colleagues that it is the malaria and not the quinine that so often untimely terminates utocia, we have always been very cautious in administering quinine to our pregnant cases, insisting upon their remaining in the hospital where they can be closely watched, and administering quinine in smaller and more frequent dosages, as for example, 5 grains every 3 or 4 hours, totalling 20 to 25 grains per day. It is certain that malarial cases must be treated despite pregnancy and if quinine is really toxic in these cases, as we believe it is, it is hoped that atebrine will be found to be definitely safer to administer in these conditions.

Dr. M. E. Durán of our hospital staff believes that in his experience the quinine seems to reduce the fever more quickly than the atebrine. "At least one day sooner" was the doctor's assurance. A perusal of my series of charts seems to confirm this observation. If this shall be proved to be substantially true then a last recommendation of this paper may be to the effect that after all, quinine had best be given for a day or two before beginning the five day atebrine treatment, including therein the plasmochin compound tablet every night.

Almost a year has transpired since the completion of this report, and our records show that during this time 10 of the atebrine series of 100 cases, and 10 of the quinine series of 100 were re-admitted for malaria. Of the

10 atebrine cases, 6 were originally estivo-autumnal and of these 3 returned with estivo-autumnal and 3 with tertian malaria. Three of these atebrine series were tertian of which 1 returned with tertian, 1 with estivo-autumnal, and 1 returned twice with tertian and once with estivo-autumnal infections. The remaining 1 of the 10 was quartan and our records show that he was readmitted with estivo-autumnal malaria. Now of the 10 cases of the quinine series which returned during this time, 5 were originally estivo-autumnal, 4 were tertian and 1 was quartan. Of the estivo-autumnal infections, 3 returned once with estivo-autumnal, 1 returned twice with estivo-autumnal, and one returned with tertian parasites. Three of the 4 tertian cases returned with tertian parasites and 1 with estivo-autumnal infection. The quartan case presented estivo-autumnal malaria on return.

In concluding, I want to thank Dr. L. M. Drennan for all of his kind coöperation in making this investigation possible, Dr. Juan Dávila for his able assistance in following up a number of the cases while taking over my service for a short period, Sr. A. E. Gil del Real and his laboratory staff for their excellent service, and coöperation, as well as the nurses who carried out the treatments faithfully and intelligently.

CORONARY ARTERY DISEASE AND ANGINA PECTORIS; THE PRESENT STATUS WITH A REVIEW OF SOME OF THE RECENT LITERATURE *

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In presenting a paper on this subject it seems advisable to begin with an explanation. For although relatively few contributions were made in the century and a half which elapsed between the epochal work of William Heberden [1] in 1768 and that of James B. Herrick [2, 3] in 1912 and 1918, a wealth of material on this theme has appeared in the world's medical literature of the last 20 years. The usefulness of an additional paper on the general subject at this time might, therefore, properly be questioned. At the risk of such criticism and with the realization that much of the material here discussed has already been presented in the collection of splendid articles recently published under the editorship of Robert L. Levy,[4] the writer nevertheless considers it worthwhile to make available in a single paper a summary of the accumulated information upon a subject of such vital and increasing importance. The attempt perhaps receives further justification from the fact that in recent years the conviction has been growing that the incidence of coronary heart disease the world over has been continually increasing,[5, 6] and that physicians are among its most frequent victims.[7, 8, 9]

Anatomical and Physiological Considerations

Although it has been repeatedly demonstrated that anatomically the two coronary arteries communicate with each other and that either artery can be injected from the other, physiologically this anastomosis must be quite limited, since occlusion of a major coronary branch almost always results in an infarct with rapid necrosis of the cardiac tissue. Furthermore, the coronary system is to a large extent isolated from the general circulation, and except for very slight and inadequate communications with the vasa vasorum of the main vessel and with the circulation of the pericardium and of other mediastinal structures, no important connections exist with extracardiac vascular territories.

The venous system of the heart is more variable in structure than the arterial. Most of the cardiac veins open into the coronary sinus, which is situated in the posterior part of the coronary sulcus and ends in the right atrium. A substantial but variable number of cardiac veins drain directly into the right atrium. Recently considerable attention has been directed to the possible importance of the Thebesian veins in the nutrition of the heart under certain pathological conditions. These veins (first described by Adam Christian Thebesius in 1708) are minute channels which

* Received for publication November 22, 1937.

arise in the muscular wall of the heart and open directly into the cardiac chambers. The majority open into the auricles; a few end in the ventricles. More than 90 per cent of the exits are on the right side of the heart.[10] It appears probable that these minute veins, normally a part of the drainage system, may under certain circumstances, when pressure relations are reversed, assume an irrigating function.[11] Such reversal of pressure gradients can occur when a large branch of a coronary artery is occluded.[10] The formation of an infarct may thus be prevented by a reversal of flow in the Thebesian channels. However, since only an insignificant number of these channels open into the left ventricle, little practical benefit to this chamber can be derived from that source. "It is no doubt this peculiar circumstance that makes infarction of the auricles and of the right ventricle so rare and infarction of the left ventricle under like circumstances so common."[10]

The coronary circulatory system is in large part enclosed by the constantly active muscle walls of the heart. Due to this circumstance, the coronary vessels are subjected to constant passive variation in their caliber. This variation in caliber and the aortic pressure constitute the major factors in the determination of the blood flow in the coronary vessels.[10] During systole the resistance within the coronary system is obviously greatly increased. However, as has been shown by Wiggers and his associates,[12] even during the phase of maximum systolic contraction, "the intramural pressure never equals the aortic pressure"; and consequently "intramural compression is not ordinarily sufficient to arrest coronary flow, but merely tends to retard it." It follows from the foregoing that although the coronary flow during systole is not completely arrested, the diastolic flow normally exceeds the systolic because the resistance is less and because the diastolic phase is normally longer than the systolic.

Coronary Artery Disease and Myocardial Insufficiency

It has been pointed out that impairment of the coronary circulation is more apt to affect the left ventricle than the right. Although sooner or later weakness of both ventricles supervenes, it not infrequently happens that symptoms of left ventricular failure are the first and for some time remain the dominant manifestations of coronary artery disease. Briefly, such signs and symptoms are of two categories: (*a*) those due to congestion of the pulmonary circulation and (*b*) those due directly to muscle impairment. Symptoms due to pulmonary congestion are (1) dyspnea (without peripheral edema), (2) paroxysmal (often nocturnal) dyspnea, (3) increased pulmonary vascular markings (roentgenographical), (4) increased pulmonary second sound, and (5) diminished vital capacity. The signs due more directly to muscle wall impairment are (1) protodiastolic gallop rhythm and (2) pulsus alternans. Of the causes which produce left ventricular failure the most important are (1) hypertension, (2) aortic

disease, and (3) coronary artery disease.[13] If hypertension and aortic valve defects can be excluded, the development of myocardial insufficiency in which weakness of the left ventricle is the dominant factor, strongly suggests coronary artery disease.

Coronary Artery Disease and Angina Pectoris

With the general recognition that coronary insufficiency is the most important cause of angina pectoris, there has been a growing tendency to regard coronary disease and the anginal syndrome as essentially the same condition. This view is not altogether justified. Although coronary sclerosis is found in the vast majority of patients exhibiting the anginal syndrome, there is a substantial number of cases, variously estimated as between 10 and 50 per cent (the former figure is probably more nearly correct), in which the syndrome is due to causes other than disease of the coronary arteries. It is also quite generally known that many patients (probably close to 50 per cent) with extensive coronary artery disease never suffer anginal pain. Coronary artery disease is a pathological entity, but its clinical manifestations are varied. Although it is often attended by characteristic symptoms, in some instances such symptoms may be entirely absent or they may be so obscure that the condition remains unrecognized throughout life. On the other hand, angina pectoris is essentially a clinical syndrome and its diagnosis is based wholly upon the history. Its pathological background varies from complete absence of anatomical changes to the presence of extensive alterations involving the coronary arteries, the heart, its valves, the aorta, the blood, or blood-forming organs.

Angina Pectoris: Etiological and Pathological Types

The essential pathological physiology underlying the anginal syndrome is believed to be an anoxemia of the myocardium. This may be brought about in the following manner: (*a*) by an obstruction of the blood channels (coronary artery disease), (*b*) by a deficiency in the quantity or quality of the blood (severe anemia, especially pernicious anemia), and (*c*) by an impairment of the mechanism, or pressure gradients, by means of which the blood is propelled into and through the coronary arteries. As pointed out above, the two most important factors which determine coronary flow are aortic pressure and the variation in intramural resistance resulting from phasic activity of the cardiac muscle. Hence, anything which interferes with adequate systolic and more especially with adequate diastolic pressure or with the length of diastole, will interfere with efficient coronary flow and produce an anoxemia. In this category are included aortic valvular disease (regurgitation or stenosis), and less commonly mitral stenosis; tachycardia, especially the paroxysmal type; and hyperthyroidism. Toxic and functional states have been regarded as possible factors producing coronary

spasm and myocardial anoxemia, but their importance is not universally acknowledged by physiologists.[10] The effect of tobacco, alcohol and other drugs and chemicals also remains disputed. From a clinical investigation in which the past habits in the use of tobacco and alcohol of 750 consecutive patients with angina were compared with similar habits of 750 patients without angina, White and Sharber [14] arrive at the conclusion that these two agents are without significant effect upon the genesis of angina pectoris. The rôle of extracardiac factors should be mentioned for the sake of completeness, but their importance in the causation of angina pectoris is relatively insignificant. I refer to aortitis [15] (without coronary involvement), and to diseases of the esophagus and stomach.[16]

Symptoms of Angina Pectoris

The characteristic symptom of angina pectoris is the sudden onset of a severe choking or throttling pain which usually originates in the upper or middle sternum, and often radiates to the left arm and hand, sometimes to other parts of the chest, and less frequently to the neck, back, and right arm. The pain is agonizing in character and is usually provoked by physical exertion, emotional excitement or by exposure to cold. Less frequently an attack may occur while the patient is at rest or may even arouse him from sleep. There is usually no apparent disturbance in the heart action. The pulse as a rule remains unchanged, although the blood pressure may rise slightly. After a few minutes, especially if nitroglycerine or amyl nitrite is administered, the attack subsides. Rarely does an acute attack last longer than 15 or 20 minutes, although some slight discomfort may continue for a half hour or longer.

Diagnosis of Angina Pectoris

The diagnosis of angina pectoris is dependent wholly upon the history. Although in many instances some cardiovascular disorders may be found, such changes are not characteristic, and in about one-fifth of the cases no abnormalities are observed upon physical, roentgenographic, or electrocardiographic examinations.[5, 17] The diagnostic triad which is usually necessary or sufficient to establish the diagnosis of angina pectoris is (1) the location and character of pain, (2) the presence of a provocative factor (exertion, emotional excitement, or exposure to cold), and (3) the brief and paroxysmal nature of the attack. But although the presence of the "anginal syndrome" is established wholly from the history, it is necessary in every instance to determine if possible the underlying pathology by routine diagnostic procedures including electrocardiographic and roentgen-ray examinations.

The differential diagnosis usually presents little difficulty. Conditions which sometimes have to be considered in such a differential diagnosis are

neurocirculatory asthenia, pericarditis, herpes zoster, tabes dorsalis, mediastinal or bronchial tumor, diaphragmatic hernias, and diseases of the bones, joints, muscles, and bursae of the upper chest.

Prognosis of Angina Pectoris

The prognosis of angina pectoris depends to a considerable extent upon the underlying pathology. As a rule the prognosis is more grave in the presence of serious anatomical changes and more favorable if cardiovascular abnormalities cannot be demonstrated. However, in many instances the patient is able to carry on with occasional attacks over a period of many years even in the presence of obvious organic disease; while in other instances death may occur during an attack, although no serious anatomical changes can be demonstrated even at necropsy. It follows that the prognosis of angina pectoris is very uncertain; for although the outlook is generally grave, a patient may live with occasional attacks for an indefinite period of time; and in some instances the attacks gradually diminish in frequency or even cease altogether.

Coronary Artery Disease: Etiological and Pathological Types

The etiology of coronary artery disease, like that of generalized arteriosclerosis, is essentially obscure. In the majority of cases the lesion is of the senile atherosclerotic type with no distinct etiological background. It may occur at any age, but it is most often observed in persons past middle life.

The influence of heredity is generally recognized. The "constitutional" factor is especially stressed by Levine.[18, 19] The "well set, stocky, strong man" with "rounded forearms" appears to be the type most apt to develop coronary sclerosis and angina pectoris.

The sex incidence also appears significant. In women coronary disease seldom occurs except in the presence of hypertension or diabetes[20]; but despite the slightly higher frequency of hypertension in women, the incidence of coronary disease among them is only about one-fourth that among men.[18, 19, 20] This latter circumstance to some extent impairs the significance of hypertension as a cause of coronary disease which would be suggested by the relatively frequent association of these two conditions in both sexes.

In a small number of cases, more specific etiological factors may be apparent. Thus coronary disease may be caused or accelerated by the presence of diabetes or gout; also special types of lesions involving the coronary arteries are sometimes encountered in Buerger's disease and in syphilis. The latter in rare instances may produce a diffuse arteritis affecting the larger or the smaller coronary branches.[21, 22] The usual syphilitic lesion affects the coronary arteries in a limited area at their ostia, generally as an extension of the same process involving the ascending portion of the aorta. Von Glahn[23] noted that the process is more apt to affect those arteries whose

orifices are "situated either at the upper limit of the sinuses of Valsalva or above this level, where the syphilitic process in the aorta usually ceases. The orifices of those arteries arising normally are seldom involved."

In recent years the rôle of disturbed cholesterol metabolism in the etiology of atherosclerosis has received much attention.[24, 25, 26, 27, 28] The ability to produce the lesion in rabbits by means of cholesterol feeding appears to have been demonstrated beyond question. Hypercholesterolemia, invariably present in the experimental lesion, is also frequently observed in clinical atherosclerosis. However, as pointed out by Anitschkow,[25] Menne,[28] and others,[27] human atherosclerosis appears to be the result of combined etiology ("combination theory" of Anitschkow) including, in addition to the disturbed cholesterol metabolism, such important predisposing factors as mechanical strain, disordered endocrine function, infection, and toxemia. Hence, in the light of present knowledge, it appears that hypercholesterolemia arising from overdosage or from other causes, although of probable importance in conjunction with the aforenamed predisposing factors, cannot be regarded as of exclusive etiological significance.

Coronary Artery Disease: Clinical Types

The variation in the clinical manifestations of coronary artery disease is dependent upon three factors: (1) the degree of coronary narrowing, (2) the rapidity with which narrowing or obstruction develops, and (3) the sensitivity of the patient, or the variance of the pain threshold. The first two factors are self-evident. The third is assumed as an explanation for the variation in the degrees of pain which attends sudden coronary occlusion in different individuals, and for the fact that in rare instances no pain at all is experienced. The clinical types thus recognized are:

(*A*) Cases of coronary sclerosis with gradual narrowing and slowly developing myofibrosis, presenting the following clinical manifestations: (1) paroxysmal attacks of angina pectoris, (2) varying degrees of myocardial insufficiency more especially of the left ventricular type, and (3) varying degrees of heart block, ectopic beats, and less frequently, other disturbances in rhythm. All of these manifestations singly or combined may be observed in any individual case; or no symptoms may be present, and the condition is found at necropsy when death results from some other cause.

(*B*) Cases of more or less sudden complete occlusion of an important coronary branch, resulting in myocardial infarction and one or more of the following clinical manifestations: (1) sudden death, (2) sudden onset of severe anginal pain which persists for a period of hours or days (status anginosus) with collapse, nausea and vomiting, fever, leukocytosis, increased sedimentation rate, embolic phenomena, pericardial friction rub, and myocardial insufficiency in which weakness of the left ventricle predomi-

nates, (3) sudden attack of acute dyspnea (cardiac "asthma") with no pain but with gradual development of myocardial insufficiency in which at the onset weakness of the left ventricle is apt to predominate, and (4) a somewhat unusual type of "occult" coronary occlusion.

In the latter no clinical disturbance occurs at the time of the occlusion, and the patient, unaware that anything serious has happened, continues about his business. In rare instances the infarct heals without ever producing clinical symptoms and remains undiscovered, or is found at necropsy after death from some other unrelated cause. More often, after a period of time, there develop gradually increasing dyspnea and other signs of myocardial insufficiency with left ventricular weakness predominating in the earlier stages.

This type of myocardial insufficiency merits special emphasis as its true nature is often overlooked. It is exemplified by the following observation. A 46 year old salesman with a negative past history and with an available record which definitely excluded syphilis, rheumatic fever and hypertension, more or less suddenly developed dyspnea on moderate exertion. He was nevertheless able to continue his usual occupation for about three months when one night some two weeks before death, he awoke with a severe attack of "asthma." Following this episode he was forced to remain in bed because of marked weakness, continuous shortness of breath, and frequent seizures of intense dyspnea. On several occasions during this illness the systolic blood pressure was found to be between 90 and 110. There was no cardiac pain, and no evidence of valvular disease was noted by the family physician. Only slight edema of the legs appeared a day or two before death. The writer was summoned for the first time one midnight during the final attack of paroxysmal dyspnea. The patient died before an examination could be made. However, the history as related above suggested the diagnosis of "painless" coronary occlusion with myocardial infarction and myocardial insufficiency primarily of the left ventricular type.

At autopsy there were found (1) an "old" recanalized thrombus of the circumflex branch of the left coronary artery with an "old" healed infarct of the posterior wall of the left ventricle, and (2) a "recent" thrombus of the anterior interventricular branch of the left coronary with extensive anemic infarction of the myocardium of the left ventricle and the interventricular septum with mural thrombosis, and acute hemorrhagic and fibrous pericarditis.

It is evident that the "old" occlusion of the circumflex branch was responsible for the early relatively mild symptoms, and that the "recent" occlusion of the anterior descending ramus coincided with the onset of the severe paroxysms of dyspnea which terminated in death ten days later. No pain was associated with either of the two attacks of coronary thrombosis.

Diagnosis of Coronary Artery Disease

From the foregoing account of the clinical manifestations of coronary artery disease it is evident that its diagnosis is suggested by (1) the occurrence of anginal attacks in the absence of serious valvular disease, severe anemia, or any of the other causes of angina pectoris described above; (2) the development of myocardial insufficiency especially of the left ventricular type, in the absence of hypertension, valvular disease, or any other discoverable cause; and (3) the occurrence of a clinically recognizable attack of acute coronary thrombosis. The diagnosis may be further confirmed by the presence of suggestive or characteristic electrocardiographic changes.

Diagnosis of Acute Coronary Occlusion

A typical attack of acute coronary thrombosis is usually readily recognized by the character of the pain and the associated phenomena tabulated below. The pain of acute occlusion, although similar to the pain of angina pectoris, differs from the latter in that it is more prolonged, is apt to be more severe, is not usually related to an antecedent provocative factor, such as exertion, emotion, etc. (in about 40 per cent of the cases coronary thrombosis occurs during sleep [29]), and is not relieved by nitrites.

The differential diagnosis of angina pectoris and acute coronary occlusion is indicated in the following table:

	Angina Pectoris	Acute Coronary Occlusion
1. Character of pain	Same	Same
2. Location of pain	Upper and middle portion of sternum	Lower part of sternum
3. Provocative factor	Usually present	Usually absent
4. Behavior	Immobile	Restless
5. Duration of pain	Minutes	Hours or days
6. Effect of nitrites	Relief	No relief, may be harmful
7. Nausea and vomiting	Absent	Usually present
8. Dyspnea	Usually absent	Usually present
9. Collapse	Usually absent	Usually present
10. Acceleration of pulse rate	Usually absent	Usually present
11. Blood pressure	Usually slight rise	Usually falls; sometimes initial rise followed by fall
12. Fever and leukocytosis	Absent	Present
13. Sedimentation rate	Normal	Increased
14. Electrocardiographic changes	May be absent	Usually present and characteristic
15. Pulmonary edema	Absent	May be present
16. Pericardial friction rub	Absent	May be present
17. Embolic phenomena	Absent	May be present

Coronary Artery Disease: Electrocardiographic Changes

In acute coronary occlusion the electrocardiographic changes are almost always sufficiently characteristic to be practically diagnostic, both as to the presence of the lesion and as to its location. This is especially true if serial tracings are available. Anterior infarction, usually located at the apex of

the left ventricle, is due to thrombosis in the left coronary artery. In the electrocardiogram it is indicated by: (1) a shift of the RS–T segment upward in Lead I and downward in Lead III, (2) inversion of the T-wave in Lead I, and increased height of the T-wave in Lead III. There is usually a diminution of the amplitude of the QRS in Lead I, and sometimes also in Leads II and III. A well-marked Q-wave sometimes appears in Lead I, and a large S-wave not present before may appear in Lead III.

Posterior infarction is usually located at the base of the left ventricle posteriorly and often involves the adjacent part of the interventricular septum. It is due to a thrombosis in the right coronary artery and is indicated in the electrocardiogram by changes essentially the reverse of those produced by an anterior infarct: (1) a shift in the RS–T segment upward in Lead III and downward in Lead I, (2) the T-wave is inverted in Lead III and remains upright in Lead I. A wide and deep Q-wave appears in Lead III and usually also in Lead II.

In either type of infarction in the course of time the RS–T segment tends to return to the isoelectric level and at the same time the inverted T-wave tends to increase in depth and width. "Just before the disappearance of the shift the RS–T segment may present an upward convexity followed by a more or less sharply inverted T-wave. It is essentially a diphasic T-wave directed first upwardly, then downwardly."[30] This is the so-called coronary T-wave of Pardee.[31] "In Leads I or II it is almost pathognomonic of coronary occlusion. In Lead III, unless accompanied by changes in other leads, it is not so significant."[30]

In the chest lead (IV) with the exploring electrode over the apex of the heart, an anterior infarct causes a disappearance of the Q-wave (normally deep and wide) and an upright or a diphasic T-wave (normally more or less sharply inverted).* "Because of the distance of the posterior surface of the heart from the chest wall, posterior infarcts are not readily revealed by this means."[30]

Coronary sclerosis without thrombosis is apt to produce irregular electrocardiographic changes involving any or all of the waves and complexes depending on the extent of cardiac muscle damage which resulted from the arterial disease. Such changes, however, are not characteristic or diagnostic, since myocardial damage from any other cause may produce similar alterations. Sometimes an entirely normal tracing is obtained in the presence of extensively diseased coronary arteries. Normal electrocardiograms have been obtained in some instances a few days and a few hours before the occurrence of an acute occlusion. Sometimes even after the occlusion,

* Since this paper was submitted for publication, the method for taking chest leads has been changed at the recommendation of the committees of the American Heart Association and of the Cardiac Society of Great Britain and Ireland, with the result that relative positivity of the chest electrode causes an upright deflection. The tracing obtained by the new method is essentially a mirror image of the old Lead IV. (Standardization of precordial leads, Jr. Am. Med. Assoc., 1938, cx, 395; Standardization of precordial leads; Supplementary report, *ibid.*, 1938, cx, 681.)

a tracing is obtained which presents little or no deviation from the normal, although several hours later typical electrocardiographic changes develop.

Preliminary of Premonitory Pain in Coronary Thrombosis

Recently attention has been called to the occurrence of substernal or epigastric pain preceding by hours or days the onset of acute coronary occlusion. This differs from the typical anginal pain, from which the patient may or may not have suffered in the past, in that it is usually milder, is not related to effort, is more prolonged, and does not significantly respond to nitrites. It is also distinguishable from the pain of actual occlusion in that it is not accompanied by any of the objective findings usually present in the latter such as fever, leukocytosis, accelerated sedimentation rate, or characteristic electrocardiographic changes.

Feil [32] noted such preliminary pain in 15 cases of acute coronary occlusion. Sampson and Eliaser [33] reported this symptom in 29 cases. These figures represent about half the total number of cases of coronary thrombosis studied by those authors over a given period.

It is often the experience of the student confronted with a newly-described sign or symptom to find, upon a search of the literature, similar observations already recorded. Sampson and Eliaser quote Herrick,[2] who as early as 1912 mentions in one of his case histories a premonitory attack of pain of unusual nature arising three days prior to the occlusion. They also note that Conner and Holt [34] and Parkinson and Bedford [35] "describe the occurrence of transitory pains in the chest of a nature different from previous anginal attacks." Levine [18] in his recent book states that "on close questioning many (patients) will confess that during the preceding day or two they had not felt quite well, and may have had more or less milder discomfort in the chest." And earlier (1929) in his monograph on coronary thrombosis Levine [19] records two case histories with premonitory pain. In one (case 39) the "patient who was always strong, vigorous and active" stated that "on the day before the severe attack there were a few premonitory anginal spells." In the other (case 120) "the interesting features were the premonitory symptoms for several days when the attacks that previously lasted a few minutes began to last a few hours." Willius [36] reported a patient with coronary sclerosis and anginal attacks of five years' duration who, on the day preceding a typical attack of coronary thrombosis had suffered "an oppressive retrosternal recurrent pain which was relieved by acetylsalicylic acid." This pain occurred while the patient was motoring and was apparently different from his accustomed anginal attacks. There were also "no abnormal findings revealed by examination including electrocardiographic study." It was Willius' opinion that "the mild recurrent retrosternal pain which occurred the day before the attack of complete coronary obstruction represented the period when the thrombus was form-

ing. These symptoms are probably dependent on the rate at which the artery becomes occluded."

The significance of this pain is not altogether established. Both Willius and Feil suggest that a gradually forming thrombus in a stenosed coronary artery appears to be the most probable cause of the premonitory pain. If this explanation is correct the development of such pain assumes important diagnostic and prognostic significance. Sampson and Eliaser [33] discuss the possible importance of enforcing bed rest immediately upon the appearance of premonitory pain, but they are unable to reach any conclusion as to the value of such enforced rest in the prevention of the final occlusion.

The Pericardial Friction Rub

The development of an audible pericardial friction rub is dependent upon (1) the location of the infarct in relation to the anterior chest wall and (2) the extension of the infarct outward so as to involve the pericardium. Although anterior infarction is admittedly more frequent than posterior, the preponderance of the anterior lesion is probably not so great as was formerly believed. In 46 autopsied cases Levine [19] found the lesion within the distribution of the anterior descending branch of the left coronary in 39 instances, or in about 85 per cent. However, in a large series of cases Willius [37] found anterior and posterior infarction in the relation of 56.3 per cent and 43.6 per cent respectively; and Master, Jaffe and Dack [38] in a clinical study of 243 patients found anterior and posterior lesions with equal frequency. It is clear, therefore, that in a large number of cases the infarct is located posteriorly and the involvement of the pericardium in this location is less likely to produce an audible friction rub. Furthermore, as was pointed out by Bedford [39] a myocardial infarct quite often extends inward and involves the endocardium; but, due to the relatively more abundant (extracardiac) collateral circulation of the epicardial surface, the infarct less frequently extends outward far enough to involve the pericardium. It follows that the pericardial friction rub, although a valuable diagnostic sign and one which should always be sought for closely, is not so common as might be inferred from the frequent reference to it in the literature. Levine [19] in his series of cases referred to above, notwithstanding the great predominance of anterior lesions, noted friction rubs in only 13.8 per cent. When present it is usually heard best at or near the apex, and generally first appears in from one to several days after the onset of the attack.

Embolic Manifestations

In consequence of the frequency with which the ventricular endocardium is involved in infarction, mural thrombosis is very common. In a recent review of the subject Blumer [40] estimates that mural thrombosis over the infarcted area occurs in about 50 per cent of the cases. In the 45 autopsied

cases of Levine's series[19] mural thrombi were found in 36 (80 per cent). Wolff and White,[41] reporting on 23 autopsied cases, state that "mural thrombosis almost always occurs over the infarcted area." However, embolic lesions recognizable clinically or pathologically are much less frequent. In the total of 145 cases reported by Levine embolic phenomena were observed (clinically or pathologically) in only 22 (15 per cent). It is apparent that fortunately in many instances mural thrombi organize without producing clinically important embolic accidents. When they so organize, they often serve to strengthen a weakened, thinned-out ventricular scar.

Since the left ventricle is more often the seat of infarction than the right, mural thrombosis occurs more frequently in the left ventricle, and emboli are more common in the systemic than in the pulmonary circulation. However, due to the relatively frequent involvement of the interventricular septum, thrombi within the right ventricle are not rare, and when present serve as a source of pulmonary embolism. Occasionally pulmonary infarction may also result from a paradoxical embolus in the presence of a patent foramen ovale; or it may arise from thrombi formed in the right auricular appendage as a result of auricular distention or auricular fibrillation.* In a series of 81 autopsied cases collected from the literature (including 35 of his own) Blumer[40] found the site of embolism to be distributed as follows: lungs 35, brain 23, kidney 6, spleen 2, extremity 8, periphery 6, and aorta one. Thus in this series the proportion of systemic to pulmonary embolism was 46 to 35.

Fever and Leukocytosis

Fever and leukocytosis occur in nearly all cases of acute coronary occlusion. They usually develop within 12 hours after the accident and gradually disappear in several days; sometimes they may persist for two weeks or longer. In exceptional cases fever and leukocytosis may never develop, or either may develop without the other.

Sedimentation Rate

The erythrocyte sedimentation rate begins to rise after 24 to 48 hours and continues to increase for several days. It remains elevated for two to four weeks or longer, and with the healing of the infarct it gradually falls to normal. In 29 cases studied by Shookhoff, Douglas, and Rabinowitz[42] the sedimentation rate was abnormally rapid in all. In two of these cases the temperature and leukocytosis remained normal throughout the illness.

The sedimentation rate is probably the most reliable index of the activity within the infarcted area including the mural thrombus. It is of both

* In some instances of coronary occlusion pulmonary embolization results from thrombi originating in the systemic veins due to slowing of the general circulation. I have also observed recently an instance of acute coronary occlusion in which on the eighth day after the onset of attack, while the patient appeared to be doing well, death occurred suddenly from massive pulmonary infarction which resulted not from an embolus but from a thrombosis of the pulmonary artery.

diagnostic and prognostic importance. In the presence of cardiac pain the failure of the sedimentation rate to rise after several days is evidence against the occurrence of infarction. In known coronary thrombosis a constantly increasing sedimentation rate is an unfavorable prognostic sign, while a gradual decrease is of favorable import.[43] The maintenance of a high sedimentation rate is an indication for continued bed rest.

Disturbances in the Cardiac Mechanism in Coronary Thrombosis

Cardiac irregularities are common. These include premature beats (auricular and ventricular), auricular fibrillation and (less commonly) flutter, heart block (varying degrees), and paroxysmal tachycardia (auricular and ventricular). These irregularities in rhythm are usually transient and as a rule require no special treatment. The pulse rate is usually rapid, although occasionally the rate may be slow even in the absence of heart block. Gallop rhythm is common and occasionally pulsus alternans is present. The last two disturbances are probably the direct result of weakness of the left ventricle.

Cerebral Manifestations in Coronary Thrombosis

Occasionally an attack of coronary thrombosis is ushered in with cerebral symptoms, including convulsions, coma, restlessness, and confusion. They may also develop at any time during the course of the illness. Cerebral anoxemia from heart block or myocardial insufficiency, cerebral emboli, and extreme collapse,[19, 44] have been suggested as possible causes of these manifestations.

Pitfalls in Diagnosis

Despite the general appreciation of the various manifestations of coronary thrombosis, there are many clinical conditions with which acute coronary occlusion is not infrequently confused and which need to be borne in mind in a consideration of the differential diagnosis. Among the more important are the following: paroxysmal tachycardia, cardiac neurosis, neurocirculatory asthenia, pericarditis, syphilitic aortitis, rupture of aortic valve, dissecting aneurysm, rupture of aorta (into pericardial sac), pleurisy, pneumonia, massive collapse, acute pneumothorax, spontaneous interstitial emphysema of lungs, pulmonary embolism, herpes zoster, arthritis of costochondral articulations, arthritis of shoulder joint, spondylitis of cervical and upper dorsal spine, tabes with gastric crises, and acute abdominal conditions including perforating peptic ulcer, acute gastritis, acute pancreatitis, gallstones and diaphragmatic hernia.[45, 46]

Although in most cases the foregoing conditions can be readily distinguished from acute coronary occlusion, there are instances in which a differential diagnosis is extremely difficult, and several days' observation may be required for its establishment.

Coronary Thrombosis, Glycosuria, and Diabetes

It has been pointed out that coronary disease is common in diabetes. However, it should be emphasized that transient glycosuria is not infrequently observed during the course of acute coronary occlusion and the diagnosis of diabetes must not be made without additional evidence.[45]

Prognosis of Coronary Thrombosis

It is now generally appreciated that a more cheerful attitude regarding the prognosis of coronary thrombosis is justified.[37, 38] Under favorable circumstances, when the condition is promptly recognized, the average immediate mortality (within the first six weeks) is probably not over 20 to 25 per cent. Recovery with resumption of normal activity for a period of years is not infrequent. White [47] recently reported an instance of survival for 25 years although four attacks of myocardial infarction occurred between the ages of 48 and 63 years. The patient finally died of congestive failure at the age of seventy-three. In general a favorable prognosis is indicated by: (1) the relative youthfulness of the patient, (2) the absence of a history of previous attacks, and (3) typical and characteristic electrocardiographic changes. Atypical electrocardiographic changes might result from multiple infarctions or from antecedent myocardial damage and therefore indicate an unfavorable prognosis. Very low amplitude of the complexes in all the leads is an unfavorable sign. Marked myocardial insufficiency with evidence of failure of both ventricles is a grave prognostic omen. The prevailing impression that a posterior infarction carries a more favorable prognosis than an anterior lesion is called into question by some recently published statistics.[38, 48] It seems probable that the difference, if any, is very slight.

Treatment

Except in cases of syphilitic origin, the treatment of coronary disease is largely symptomatic. The therapeutic indications are thus dependent upon the prevailing manifestations, of which the most important are (1) angina pectoris, (2) acute coronary thrombosis, and (3) myocardial insufficiency.

Treatment of Angina Pectoris. It is generally agreed that the acute attack of anginal pain is most readily relieved by the prompt removal of the provocative factor (cessation of physical effort, etc.) and by the use of *nitrites.* Nitroglycerine in small doses ($\frac{1}{250}$ to $\frac{1}{150}$ grain) is generally preferred. When chewed and swallowed, its action begins within one or two minutes and continues for a half hour or longer. If necessary this dose may be repeated at intervals of 15 to 30 minutes for several hours. To assure success the preparation must be fresh and quickly soluble. A supply from a recently opened container should be procured at least every two months. When nitrites are not available, or sometimes in addition to

nitrites, *alcohol* may prove useful.[49] It may be administered in the form of whiskey or brandy in doses of one to two ounces.

During the intervals between attacks the patient's mode of life is so regulated as to avoid undue physical and emotional strain. At the onset of the illness it is often helpful to institute bed rest for a week or 10 days. However, after an initial rest period, in order to maintain the patient's morale, it is important to encourage the continuation of the accustomed occupation provided that occupation does not involve undue physical or emotional strain. Overeating should be strictly avoided at all times and if the patient is well nourished a slight loss of weight is often beneficial.

The presence of abnormalities such as obesity, hypertension, and focal infection calls for appropriate measures. Likewise special therapy is required in the presence of more specific etiological factors such as syphilis, diabetes, pernicious anemia, paroxysmal tachycardia, aortic valvular disease, and hyperthyroidism. Syphilis and diabetes should be treated with particular care. In the latter insulin is employed very cautiously, as it is important to avoid sudden wide fluctuations in blood sugar levels. In the former the bismuth preparations and iodides are preferable to the arsenicals, at least for the first three or four months of treatment.

Of the various drugs employed during the intervals between attacks some are of established benefit; others appear to be of questionable value. *Nitroglycerine* in small doses ($\frac{1}{400}$ to $\frac{1}{200}$ grain) taken four or five minutes before some necessary effort may serve to prevent an attack. In severe cases where attacks occur at frequent intervals upon slight exertion or even at rest, nitroglycerine ($\frac{1}{500}$ grain) taken at hourly intervals throughout the day may prove useful.[50] *Erythrol tetranitrate,* because of its slower and more prolonged action, is preferable to nitroglycerine for the purpose of preventing nocturnal attacks. It is given at bedtime in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain.

Although a difference of opinion exists concerning the efficacy of the *xanthine derivatives* in coronary disease and angina pectoris,[50, 51, 52, 53] the weight of clinical evidence distinctly favors their continued employment. In a recent study of the comparative value of the various preparations Brown and Riseman[53] found theobromine with sodium acetate ($7\frac{1}{2}$ grains three times daily) and theophylline with sodium acetate ($2\frac{1}{2}$ grains three times daily) the most effective. Theophylline, aminophylline, and theobromine calcium salicylate (theocalcine) were found to be relatively less effective. Occasionally, however, theobromine calcium salicylate proves effective when the patient fails to respond to any of the other preparations. If necessary the administration of a suitable xanthine preparation may be continued with or without brief interruptions over long periods of time. Untoward effects are very rarely observed.

Recently Riseman and Brown[50] found *quinidine sulfate* "of distinct value for patients who have cardiac pain while at rest or when in bed."

This drug (in doses of 5 or 6 grains three times daily) is recommended for patients who fail to respond to the nitrites and the xanthine derivatives.

For the purpose of inducing sleep and lessening restlessness, in this, as in any other serious illness, the *barbiturates* are valuable. However, no specific effects upon anginal pain can be claimed for them. There appears to be no rational basis for the employment of such compounds as "theominal" (theobromine with phenobarbital) and "theamin with amytal." The indications for each of the ingredients contained in such compounds are quite distinct; theobromine is most beneficial when continued over long periods of time, whereas barbital should be used only in single doses at rare intervals. Recently considerable evidence has been presented tending to prove that all the barbitals possess toxic side actions upon living tissues,[54] and their prolonged use should be discouraged.

Treatment of Acute Coronary Thrombosis. It is generally agreed that in the acute stage the two most important measures are *rest* and the administration of *morphine*. Morphine is especially valuable for it not only lessens the exhausting, agonizing pain and the extreme restlessness, but it also, in some indirect way, favorably influences the function of the left ventricle and diminishes the tendency to pulmonary edema and cardiac asthma. To accomplish these results large doses may be required, often as much as a grain (in divided doses) in a few hours.

Rest should be prolonged. A period of six to eight weeks in bed is generally regarded as a minimum requirement; for this is the average length of time necessary for the healing of the infarct. At the end of such period of bed rest, if the progress is favorable, adequate healing is indicated by (1) the maintenance of a normal temperature, (2) the absence of leukocytosis, (3) the return of the sedimentation rate to normal levels, (4) the absence of pain, and (5) the absence of all signs of myocardial insufficiency. Under such circumstances gradual resumption of activity is permitted.

A highly restricted *diet* is advocated by Master, Jaffe and Dack.[38, 55] Only small quantities of milk, orange juice and glucose are allowed during the first week; and then, if improvement takes place, the diet is increased to 800 calories per day, at which level it is maintained during the entire period of convalescence. Although this regime may be helpful in the excessively nourished individuals, it does not appear advisable to enforce such drastic undernutrition routinely in all cases. However, overfeeding must always be avoided, and moderate food restriction is desirable in most instances.

During the early course when shock and vomiting prevail, it may become necessary to withhold food completely. At this stage, provided there is no engorgement of the lungs and the systemic veins, the intravenous administration of *glucose* in hypertonic solutions is undoubtedly of value. It is also possible that this procedure may tend to increase the coronary flow and thus exert a more direct beneficial effect upon the nutrition of the heart.[56] After vomiting ceases, glucose in liberal amounts is given orally. The

caloric value of the glucose thus administered is taken into consideration in connection with the total daily caloric allowance.

Oxygen in concentrations of 50 to 60 per cent is advocated by Barach and Levy.[57] The chief indications for its use are (1) cyanosis, (2) marked dyspnea, and (3) pain not relieved by morphine. Although a valuable remedy its administration is sometimes difficult because of the discomfort which often attends the use of either the tent or the nasal catheter. If those difficulties can be successfully overcome it is desirable, on the average, to maintain its use for about five days, after which, if improvement is noted, the oxygen is discontinued. It is important to lower the concentration of the gas gradually before it is completely withdrawn.

Aminophylline both by the oral and the intravenous route is widely employed. Although, as already stated, the weight of clinical evidence favors the continued use of this (or a similar) preparation as a coronary dilator in angina pectoris, the value of aminophylline in acute coronary thrombosis is open to question. Recent studies seem to indicate that this drug does not significantly improve the collateral blood supply to an ischemic area, and that at least in experimental animals, daily injections of fairly large doses fail to exert any influence that can be considered favorable on the course of the infarction.[58, 59]

The position of *digitalis* in the therapy of acute coronary thrombosis is controversial.[19, 38, 55, 60, 61] The majority of experimental studies[62] indicates that digitalis causes a slight constriction of the coronary vessels and consequently retards the coronary flow. However, in the presence of congestive failure it is probable that the improvement in the cardiac function which follows the use of digitalis more than compensates the constrictive effect of the drug upon the coronary vessels. Fishberg, Hitzig and King[63] in a clinical study of 59 patients with recent myocardial infarction point out that in this condition two distinct mechanisms participate in the derangement of the circulation: (*a*) shock or peripheral circulatory failure which tends to lower the pressure in the systemic veins, and (*b*) heart failure which tends to cause engorgement of the lungs and to raise the systemic venous pressure. The former mechanism is more apt to prevail at the onset of the attack; congestive failure more often develops some days or weeks later. The extent of the infarction and the condition of the myocardium prior to the onset of the occlusion probably are additional determining factors of the type of circulatory derangement more apt to predominate. Fishberg and his associates thus suggest that the employment of digitalis in myocardial infarction may properly be determined by the prevailing type of circulatory failure. In the presence of shock associated with low venous pressure there is no indication for the use of this drug; its administration under such circumstances might indeed be harmful. On the other hand in the presence of congestive failure, the cautious use of digitalis is probably helpful.

The *nitrites,* so useful in angina pectoris, appear to be of no value in acute coronary occlusion. Furthermore, there is suggestive evidence that

the use of these drugs in acute coronary occlusion tends to increase the size of the infarct and may thus be distinctly harmful.[38, 64, 65, 66]

The place of *epinephrine* in the therapy of coronary disease appears paradoxical. Levine, Ernstene and Jacobson [67] have shown that in patients subject to anginal pain an attack can be induced by means of epinephrine. Experimentally, by intravenous or intramuscular injections of epinephrine, electrocardiographic changes have been produced closely simulating those encountered in angina pectoris and in coronary occlusion.[68, 69] In view of these facts the drug can hardly be regarded suitable for use in acute coronary occlusion. Nevertheless, Levine [18] has used it frequently for the treatment of heart block complicating coronary occlusion. In several instances he has "given 0.3 to 0.5 c.c. of adrenalin every two hours for 48 hours to patients who had this condition and thereby prevented the pauses of the heart that were otherwise occurring, finally observing that the tendency to syncope had disappeared." The writer's experience with epinephrine in coronary disease has been unfavorable, and in his opinion the use of this drug in myocardial infarction should be reserved for such emergencies as extreme shock or cardiac standstill.

Quinidine has been found useful in the treatment of paroxysmal ventricular tachycardia.[70] Although, like the other cardiac arrhythmias in coronary thrombosis, this arrhythmia in most instances is transient and tends to disappear spontaneously after a few hours, occasionally it may persist and present an important therapeutic problem. Quinidine appears to be the only drug that can control it. The dose is variable. In some instances the arrhythmia is abolished by a single dose of 5 grains; in others much larger amounts of the drug may be required.

Treatment of Myocardial Insufficiency. With the exception of the especial care concerning the use of digitalis, which has already been discussed, the management of myocardial insufficiency of coronary origin does not differ in any essential respect from the treatment of congestive failure due to any other cause. A full discussion of this phase of the subject is deemed beyond the scope of this paper. However, it may not be out of place again to call attention to the value of digitalis in the treatment of left ventricular failure before there is failure of the right ventricle. This stage is characterized by dyspnea without peripheral edema. The dyspnea may be more or less continuous, or it may appear in severe paroxysms (cardiac "asthma"), often at night. For the acute attack morphine is the most effective agent; in plethoric individuals venesection is also helpful. Intravenous administration of aminophylline is widely advocated, "but although that procedure is of undoubted value in Cheyne-Stokes breathing, its usefulness in acute paroxysmal dyspnea is not equally apparent."

After the acute attack is controlled, the continued use of digitalis is believed to be the most effective means of restoring the function of the left ventricle and preventing acute paroxysms of dyspnea. The best results are obtained from slow but complete digitalization followed by a daily

maintenance dose of approximately 1½ grains of the powdered leaves. Although this use of digitalis has already been stressed by many authors [13] the writer is convinced that the importance of this therapy is not yet generally appreciated and that its renewed emphasis at this time is justified.

Surgical Measures

In closing it is desired to call attention to the recent progress in the surgical treatment of angina pectoris and coronary disease. Generally speaking such therapy is as yet reserved for desperate cases in which relief cannot be obtained from medical treatment. Of the various surgical procedures, the one whose usefulness is definitely established and which may be said to have passed the experimental stage is the paravertebral alcohol injection of the four or five upper dorsal sympathetic ganglia.[71, 72, 73] The procedure is reasonably safe and is effective in a very high percentage of cases. If the pain is referred to one side only, unilateral destruction of the ganglia on that side is generally sufficient to control it. If the pain is referred to both sides, or if it is felt just under the sternum, bilateral injection is required. For a description of the method of performing these injections the reader is referred to the very lucid and splendidly illustrated article by James C. White.[71]

Total thyroidectomy for relief of cardiac pain [74, 75, 76, 77] and the development of a new blood supply to the heart by grafting tissues (pectoral muscles or omentum) onto the myocardium [78, 79, 80, 81, 82] are still in the experimental stage. The latter method is particularly promising. It differs from all the other modes of treatment in that it is an attempt actually to reverse the pathological process by restoring the lost blood supply to the heart muscle. Up to the present time (July, 1937) Beck [83] has performed this operation upon 25 patients; "in the first 14 cases the mortality was 50 per cent, and the last nine cases have been carried through without a fatality." Beck considers the results as very favorable. "All the patients have been improved; the improvement consists of reduction of pain and increased toleration for exercise. Three patients have been completely relieved of pain and consider themselves cured." [83]

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THE MECHANISM OF HEAT LOSS AND TEMPERATURE REGULATION *

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THERE have been surprisingly few studies dealing with the mechanism of heat loss. Heat production has received more than its share of consideration because it is really the balance between production and loss that determines the body temperature.

The Russell Sage Institute of Pathology happens to possess a respiration calorimeter which measures production and loss from the human body simultaneously but independently. This instrument, which was moved from Bellevue Hospital to New York Hospital in 1932, has been used in the study of patients with fever and many normal controls under varying atmospheric conditions. We directed our attention almost entirely to production until about 1929 when we began to realize that it was necessary to study the details of heat loss. The factor of loss by conduction of heat through solid bodies was so small in our calorimeter bed that it could be neglected. Likewise, the factor of warming food was insignificant. Vaporization of water from skin and lungs which usually accounted for about one-quarter of the heat loss was easily measured. Radiation and convection which accounted for the remaining three-quarters presented great difficulties. We measured them together but could not separate them until 1934 when Dr. James D. Hardy perfected his radiometer and surface thermometer.

The human body under ordinary conditions loses about 60 per cent of its heat by the radiation of infra red waves which travel in straight lines with the speed of light until they strike the walls of the calorimeter or room. The amount of radiation depends on the profile surface of the body and the average temperature difference between the surface of the skin and the walls. It can be measured by determining the radiating temperature of 20 different spots on the body and the radiating temperature of the walls. Using the Hardy radiometer this can be accomplished in two or three minutes. When the calories lost in radiation are subtracted from the total lost by radiation plus convection we measure the convection by difference. Convection currents of air caused by the warmth of the body remove about 12 to 15 per cent of the total heat when a man is quiet. If he exercises the increased fanning effect may double or triple the amount of heat lost in warming the air.

On the basis of a large number of detailed studies in the calorimeter it has been possible to construct a diagram which represents a balance with

* Read before the American College of Physicians, New York, April 4, 1938.

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heat production on the left pan and heat loss on the right. When the two are in equilibrium the pointer rests at 37° C. When the pans are unequally weighted the pointer swings to abnormally high or abnormally low temperatures. The load of heat production rests on the supporting legs of carbohydrate, fat, and protein, since it is only through the combustion of these substances that heat production is possible. The load of heat loss rests on the factors of convection, radiation, and vaporization.

Under basal conditions the loads on the two pans are small and are easily balanced. Moderate increases in the heat production may be caused by the stimulating effects of food, so-called specific dynamic action; by disease, if accompanied by a higher metabolism; or by the unconscious tensing of the muscles caused by emotion or by an approaching chilliness. Of

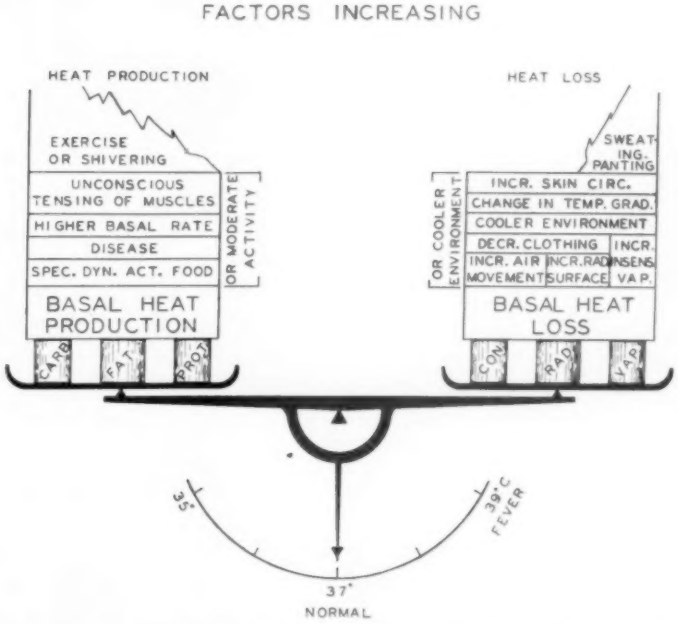

FIG. 1. Balance between the factors increasing heat production and heat loss.

course the moderate increases in heat production are ordinarily due to moderate muscular activity.

Usually these moderate increases in heat production are nicely balanced by factors increasing heat loss. The man decreases the amount of clothing, seeks a cooler environment or a place where there is increased air movement. Children spread out arms and legs to extend the radiating surface. With augmented heat production the insensible vaporization from skin and lungs increases with equal pace. If these adjustments are not sufficient the body is able to lose more heat by increasing the circulation in skin and subcutaneous tissue, thus changing the temperature gradient and bringing warm blood close to the surface. Although this flushing of skin is striking both

to subject and clinical observer the effect is limited, as a rise of one degree in skin temperature in the average sized man at ordinary room temperature can account for an extra loss of only 14 calories per hour.

It is interesting to consider what happens when a balance which has been established under basal conditions is disturbed by a moderate rise in heat loss, due to cooling of the environment or decreased clothing or any of the other factors which we have indicated on the right hand of the diagram. The body does not respond by a higher basal rate but there is, after a short delay, a higher total metabolism due to conscious or unconscious use of the muscles. If the increased heat loss be considerable the balance will swing and the pointer indicate a subnormal temperature. This can be corrected only by violent exercise or by shivering.

If, on the other hand, heat loss has remained constant and heat production has been raised suddenly by violent exertion, such as running, the factors of heat loss which were sufficient under moderate conditions are no longer capable of maintaining balance. Body temperature rises slightly, and then there is a sudden outbreak of sweat. It is the great rise in vaporization that restores the balance. Increased convection helps a little, but inasmuch as the skin temperature falls, radiation is diminished.

Another set of conditions occurs in hot weather. As soon as the temperature of the air and of the surroundings rises to a level which equals surface temperature, 35° C. (95° F.), radiation and convection cease to function as channels of heat loss. Vaporization must bear the entire burden no matter how small or how great the heat production. If the humidity be high vaporization is suppressed and body temperature rises. This is a fairly good combination for producing artificial fever but there is a better one. If the temperature of the air and walls be raised above that of the surface of the body, the gradients are reversed and the usual factors of loss are turned into factors of gain.

How is it that under ordinary conditions of life body temperature is maintained so nicely at 37° C., a little lower in the morning, a little higher in the evening? There is probably a good deal of local adjustment in various parts of the body but the finer control seems to be in the hypothalamus. In disease the thermo-regulator may suddenly be set at a higher level. Suppose in our balance diagram the body established a new "normal" at 39° C. The pointer at 37° C. would then be two degrees too low and the body would suddenly need about 120 calories in order to bring the temperature of the mass of tissue up to this new level. The only way it could accomplish this rapidly would be by shivering. Once the body had been warmed to the new level another balance could be established. If the change in the adjustment of the temperature regulating center be made slowly, shivering is not necessary, as minor adjustments in the factors increasing heat production or decreasing heat loss can accomplish a change of 2° C. in a few hours.

The result of a sudden increase in heat production is well demonstrated in a diagram showing what happened in a game of squash lasting 36 minutes. Two of the staff who were excellent players and evenly matched were studied at 12 minute intervals during exercise and the period of recovery. Figure 2 shows the results on one man who had served as a normal control in many calorimeter experiments. The rectal temperature, skin temperature, and

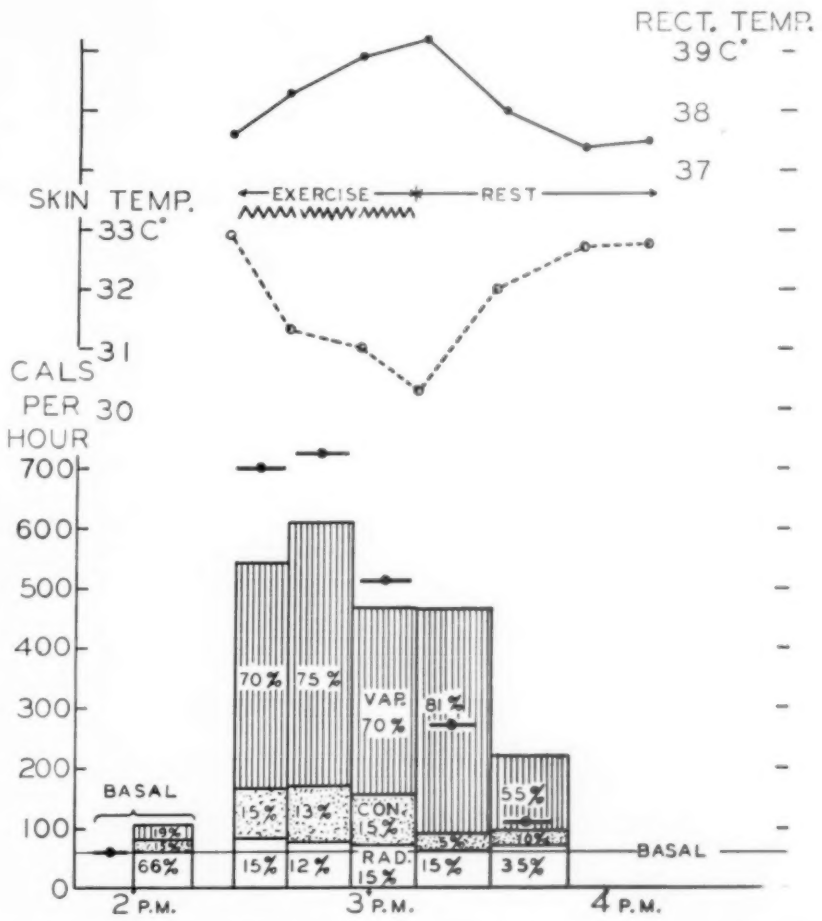

FIG. 2. Violent exercise in 36 minutes of squash racquets as shown by zig zag lines. Heat production is indicated by dots with short horizontal lines, heat loss by columns divided into radiation, convection, and vaporization. Note rise in rectal temperature and fall in skin temperature with rapid restoration to normal.

radiation were determined accurately. On the diagram the short horizontal lines with dots in their centers represent heat production, the columns show heat loss divided according to our estimation of the amounts dissipated in radiation, convection, and vaporization. During exercise heat production exceeded loss by such a great margin that the rectal temperature rose to

39° C. After the game the players rested, the loss exceeded the production, and the temperature fell to normal almost as rapidly as it had mounted. The skin temperature dropped with the first outbreak of sweat and continued to fall rapidly. This meant that the total heat lost in radiation was actually diminished although the skin was flushed with blood. Convection was increased as the man rushed about the court but it was evident that vaporization had to account for 70 to 80 per cent of the loss. The cooling must have taken place very close to the surface as the subcutaneous tissue was

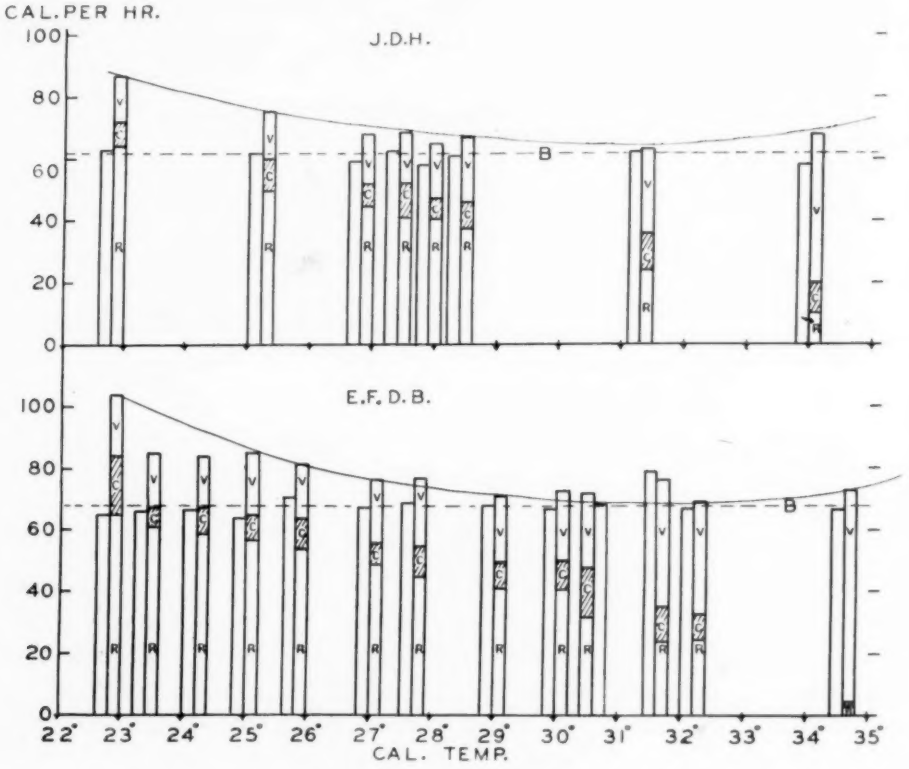

FIG. 3. Heat production (blank columns) and heat loss (columns divided to show radiation, convection, and vaporization) of two normal men, naked, under basal conditions in the calorimeter, exposed to air at temperatures between 22° C. and 35° C. The dotted line B shows the average basal metabolism.

receiving blood at a temperature of 39° C. while the surface temperature averaged 31° C., a gradient of 8° C. in a few millimeters. When the game started the difference between rectal temperature and skin temperature had been only 4.5° C.

We have made a series of studies on naked normal controls at temperatures from 22° C. to 35° C. Figure 3 shows the results on a man under basal conditions. His heat production was the same throughout

the range in spite of the fact that he was on the verge of shivering at 22° C. and was losing all of his heat through sweating at 35° C. His proportion of heat lost by radiation decreased steadily as the difference between skin and wall temperature diminished.

When a man is exposed naked and motionless and empty of food to ordinary room temperature he loses much more heat than he produces and his skin and subcutaneous tissues become colder and colder. The rectal temperature begins to fall. When a certain amount has been lost the temperature regulating center urges the man to exercise and if he, for experimental purposes, remains quiet the center will suddenly call for a chill. Figure 4 shows that under normal conditions the chill came after the average body temperature had dropped about 0.7° C. In three experiments a drink of brandy postponed the chill and allowed the body to cool off, perhaps to a

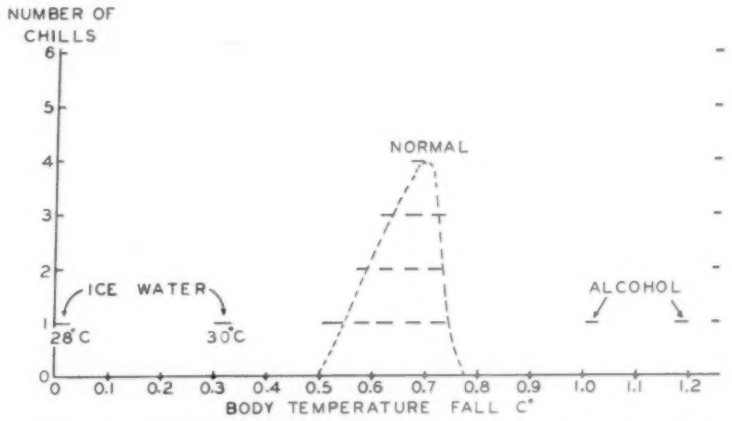

FIG. 4. Diagram showing the fall in the average body temperature before the onset of a frank chill. Under normal conditions the chill comes after a drop of about 0.65° C. Alcohol postpones the chill, ice water in the stomach precipitates a chill abruptly.

dangerous extent. In one experiment a drink of ice water given to a woman who was not due to have a chill for about two hours precipitated shivering before the body temperature had time to drop more than 0.01° C.

Chills resulting from excessive cooling of the body resemble in almost every respect chills which occur at the onset of fever. Figure 5 shows what happened after an exposure, naked, in the calorimeter at 22° C. The average skin temperature fell to 29.5° C., the rectal temperature fell 0.4° C., and the average temperature fell 0.73° C. There was a sudden chill lasting 18 minutes and this raised the skin temperature until the man was fairly comfortable. Skin temperature dropped again and a second chill caught him as he was being taken out of the calorimeter.

I cannot help showing once more the results obtained in 1918 by Dr. David P. Barr and myself on the patient George S. who kindly obliged us by having a malarial chill in the calorimeter. When the chill came the heat

production increased from 80 calories to 230 calories an hour, but the heat loss was maintained at the previous basal level. All the extra heat was stored in the body. The temperature was raised to 41° C. and balanced at this point for an hour or so. Then the temperature regulator was apparently readjusted to a normal of 37° C. and the body, finding itself 4° too warm, poured out sweat until vaporization had cooled the tissues.

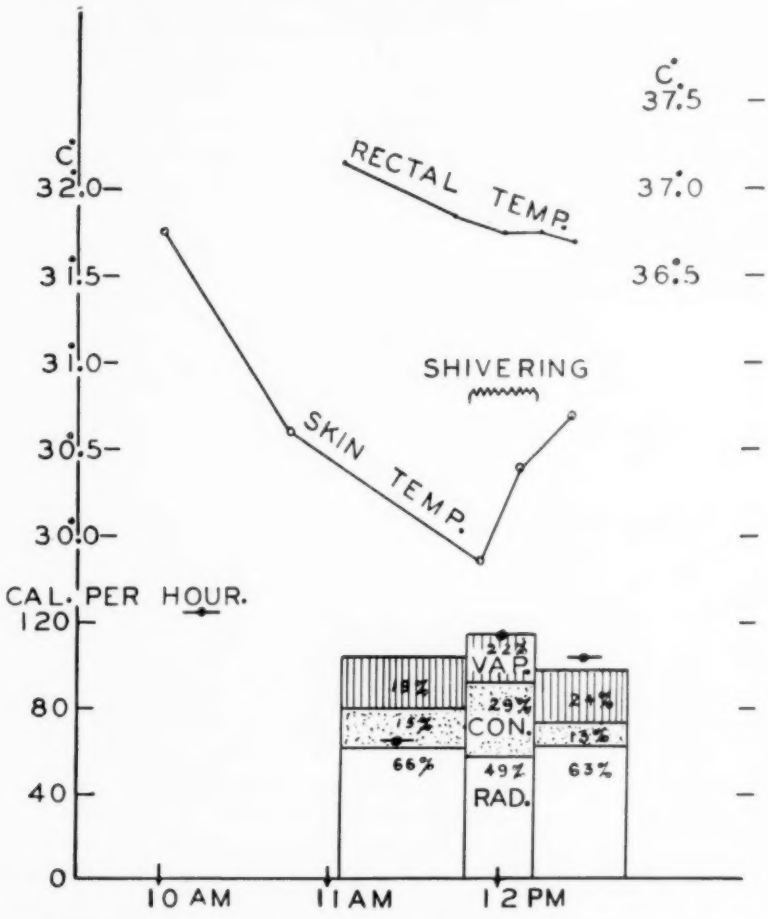

FIG. 5. A chill caused by exposing a naked man to a temperature of 22° C. Heat production indicated by dots with short horizontal lines. Heat loss in columns.

Throughout this paper I have repeatedly called attention to the fact that the skin is responsible for almost the entire heat loss. It is beautifully constructed and beautifully regulated for this purpose, and if you study it carefully you can find out what the body is doing. There is an old dictum that it is easy to measure skin temperature but hard to know what to do with the results. Dr. Hardy says that it is very difficult to measure skin temperature accurately but the results give much information. He has

demonstrated that the older methods of estimating skin temperature by thermocouples placed in contact with the skin are unphysiological and inaccurate. It is impossible to estimate the average temperature of the surface unless readings are made in many places, and the most deceptive places to measure are the hands and feet. The hands respond too quickly to emotion, the feet cool off too rapidly. Often we have found in normal persons with no change of rectal temperature a marked drop in the temperature of the toes until they were cooler than the surrounding air. On one occasion during a chill we obtained several readings of skin temperatures higher

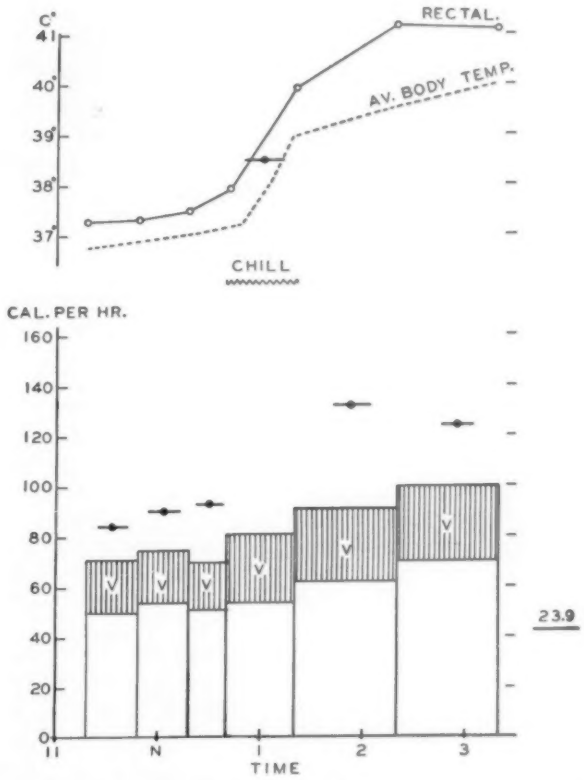

FIG. 6. A malarial chill. A redrawing of the diagram of the patient George S. studied by Barr and Du Bois.

than rectal temperatures. It is necessary to remember that a man of average size has about 15 kg. of tissue within one centimeter of the surface. This surface layer may change its temperature at a different rate and even in a different direction from the rectal temperature. After all, the rectal thermometer or the mouth thermometer only tells us what is happening in one small area during a few minutes of the day and gives the clinician merely an approximate idea of what has been accomplished as the body tries to balance or readjust heat production and heat loss.

CASE REPORTS

LYMPHATIC LEUKEMIA OF TWENTY-FIVE YEARS' DURATION *

By Charles W. McGavran, B.S., M.S., M.D., F.A.C.P., *Columbus, Ohio*

The following is a report of a case of chronic lymphatic leukemia and associated with it, a mild diabetes and a progressive cardiovascular disease. It is of unusual interest because of the duration of life after the discovery of the leukemia. Data concerning the duration of life after the onset of chronic lymphatic leukemia are quite meagre. Minot and Isaacs [4] in 1924 report on the duration of life in 87 cases the longest of which was under observation 22 years. The case here reported was observed 25 years and all this time the patient was under the personal observation of the author.

F. C. first presented himself on December 21, 1905, at the age of 48. He was married and a banker. During a recent life insurance examination, sugar had been found in the urine. He was apprehensive and complained of a sense of fullness in the epigastrium accompanied by acid eructations. His father had died at 70 of cancer of the stomach and his mother at 70 from congestive heart failure preceded by hypertensive heart disease. There were three brothers, one of whom died of spinal meningitis and a second one who died of tuberculosis at the age of forty-five. The third was living but asthmatic. There were two sisters, one of whom died in infancy of pneumonia and the other was living and healthy. His previous health was good. He had had no serious illness. At the age of 33, he had suffered from eczema followed by a series of boils. His height was 5′ 8″, weight 185½ pounds. Blood pressure was 154 systolic and 70 diastolic. His chest was large. Cardiac dullness was well within normal limits. Heart tones were clear. Lungs were negative. Abdomen was large.

During the five succeeding years, he was seen only occasionally. He had two or three attacks of acute bronchitis. He had a tremor to his hands which persisted throughout his life. During December of 1910, sugar was again found in his urine and it persisted throughout the month, varying from 1 to 2 per cent.

Because of his indigestion manifested by acid eructations and a sense of fullness in the epigastrium which progressively increased in intensity, he was referred on January 24, 1911, to the late Dr. John H. Musser of Philadelphia, who reported as follows: "He has intermittent glycosuria, which is, in all probability, secondary to a sclerotic pancreas and liver associated with and perhaps dependent upon cardiovascular conditions. It is interesting to note a leukocytosis of 18,960, and a great increase of lymphocytes, as follows:

Polys	36%
Small lymphs	42%
Large pale mono	
Transitional	20%
Eosinophiles	2%

* Received for publication September 23, 1937.

This is a lymphatic type of leukemia which I have seen accompanying intermittent glycosuria or, perhaps, better say, intermittent glycosuria as seen in lymphatic leukemia."

On January 29, 1911, he was seen by Dr. E. P. Joslin of Boston who reported as follows:

"Hemoglobin	100%
White blood count	23,200
Differential count of 200 cells:	
Lymphocytes, mostly large	93%
Polynuclears	5%
Transitional	2%
No blasts or stippling.	
Nothing abnormal with the reds.	

"The exact proportion of the white corpuscles evidently varies somewhat from day to day. I am not especially apprehensive of this finding in Mr. C.'s case and have said nothing to him about it. I think that it would be well to examine the blood again in the course of a month. My physical examination corresponds in general with what had been previously observed. The left border of the heart was 1 cm. inside the mammillary line, no murmurs, and I made the blood pressure 150 mm. mercury. There were no palpable cervical, axillary or inguinal lymph nodes. The abdomen was negative except that I could just touch the spleen and, therefore, considered it a little large."

Both consultants recommended that nothing be said to the patient about his blood condition, that no therapy of any kind be attempted and that his blood be examined at rather infrequent intervals and the symptoms be treated as they developed. Dr. Joslin saw him every few years and directed the line of management.

In March 1917, Dr. Joslin referred the patient to Dr. George R. Minot of Boston who reported in part as follows:

"Hemoglobin	100%
Red count	5,100,000
White count	25,500
Platelets	160,000

Differential count of 400 cells excluding 'smudges'! (If these were counted and considered of lymphoid origin, note that the percentage of lymphocytes would be higher).

Polynuclear neutrophiles	19%
Small and medium lymphocytes	68%
Large lymphocytes	8%
Large mononuclear cells	4.2%
Eosinophiles	0.5%
Mast cells	0.2%

"I am inclined to consider the condition chronic lymphatic leukemia on account of the continued elevated and gradually rising white blood cell count over a period of six years with persistent and apparently increasing lymphocytosis and on account of the abnormality of many of the lymphocytes. The diminution of the platelets also favors this diagnosis. . . . I am rather inclined to believe that, as the process seems to have been so chronic and relatively mild, it will continue a long time without much additional severity although, I suppose, it is equally possible that it might 'burst into flame' at any time and become severe and more rapidly progressive. . . . I do not see that there is any treatment for the blood condition that would be of any benefit or distinct advantage at the present time. . . . I am rather inclined to believe that it would be better to leave things alone and not stir them up."

In 1911, the spleen could just be touched on deep inspiration. It gradually increased in size but was never larger than to extend three fingers below the costal

margin. It always became smaller and less distinctly palpable following irradiation which was first given in June 1926. For many years, there were no palpable superficial lymph nodes. In April 1917, the inguinal nodes were first palpable, the size of a bean. They gradually increased in size but never became larger than a hazel nut. In 1918, one small lymph node, the size of a B. B. shot, was just palpable above the left clavicle. At the same time, the axillary nodes became palpable, the size of a bean. They remained palpable thereafter but did not increase in size. In May 1927, in making a rectal examination, a node, the size of a hazel nut, was felt just posterior to the prostate. There was never a noticeable increase to its size.

Very soon after the leukemia was discovered, the patient began to have looseness of the bowels. These attacks were usually controlled by dietary regulation and castor oil. Later it was necessary to give a mild opiate from time to time. In May 1926, the diarrhea had become very severe. The remedies which had formerly helped him gave him no relief. He lost much in weight and was quite weak.

He was again seen by Drs. Joslin and Minot and Dr. Minot reported as follows: "I am strongly inclined to believe that the diarrhea, which he has, is directly dependent upon his leukemia. It is, I think, not at all unusual for these patients to develop the sort of diarrhea he has had dependent upon leukemic lesions throughout the small intestines. . . . I noticed a considerable number of young lymphocytes rather large in size, which broke up very readily. There occurred a few lymphoidblasts and about 10 per cent definitely abnormal immature forms of lymphocytes. Among the smaller lymphocytes, I noticed signs of youth. I found only about 5 per cent polynuclears; 7 per cent cells which may have been monocytes; the remaining cells, except for a very rare eosinophile, were lymphocytes of all ages, there being rather more immature ones than normal ones. This blood picture suggests to me an increased activity of his disease in recent months. This is consistent with what I think is taking place within the intestinal tract. . . . By and large, he seemed in very good condition but I feel sure that it would be wise for him to have at least one full sub-erythema dose of deep roentgen-ray. I advise this to be given over the splenic area, the total sub-erythema dose being divided into four treatments. Then three or four weeks thereafter, if improvement has not occurred, I should advise another sub-erythema dose over the chest, aiming simply to irradiate a large blood area."

Irradiation

In June 1926, he received the deep roentgen-ray therapy as directed. The diarrhea responded immediately. The white blood cell count came down gradually from 67,500 on June 9, to 35,000 on July 1, and 22,000 on July 29. He felt very much better and spent the winter in California and the summer of 1927 in England. In September 1927, the diarrhea returned and he was again irradiated. This course of treatment was followed by a marked fall in the white blood cell count. On September 22, 1927, the white blood cell count was 44,000 and on the fourteenth of October, 7,000 with polynuclears 32 per cent and lymphocytes 68 per cent. The diarrhea again responded and he felt much better in every way. The irradiation was repeated in September 1929, again in 1930, 1932, and in 1934. These treatments were always followed by a marked fall in the white cell count, an abatement of his diarrhea and an improvement in his general condition. His skin, which was usually dry and scaly, would become moist and soft. At the time of his death, Mr. C. was doing well from the standpoint of his leukemia. The last blood examination, made one year after the last irradiation or two months before his death, showed the white blood cells to be 12,000 with 86 per cent lymphocytes.

In January 1932, Mr. C. was examined by Dr. B. K. Wiseman of the College of Medicine of the Ohio State University. Dr. Wiseman found that the lymphatic curve, which when normal (according to previous studies [1]) illustrates that in lymphopoiesis the lymphocytes are delivered to the peripheral blood in half-hour cycles,

was completely arrhythmic as is usually found in leukemic states.[2] The analysis of the qualitative aspects of the lymphocytes indicated an average Y–M–O (young-mature-old) formula of 13%–48%–39% (normal 5%–47½%–47½%) with many pathologic types of lymphocytes similar to those found in other cases of chronic lymphatic leukemia.

The accompanying chart shows the high and low percentage of hemoglobin found each of the 25 years and records the high and low white blood cell count, percentages of lymphocytes, and body weights for the same period. It is needless to say that there were many other blood examinations made. It is to be noted that the leukemia progressed very slowly and had it not been for his cardiovascular complications, Mr. C. would probably have lived for many more years.

Anemia

Throughout the first 15 years of observation, the patient's red blood cell picture was normal. Whether coincident or not, signs of anemia appeared in 1926 following the first irradiation. On June 10, 1926, before the first roentgen-ray therapy, the

Date		Hemoglobin (Sahli) %	White Blood Count 1000 cu. mm.	Lymphocytes %	Weight Lbs.	
1911	High	100	24.7	95.	182	
	Low	80	14.3	62.	166	
1912	High	95	27.1	84.5	170	
	Low	90	19.2	78.	163	
1913	High	100	29.	88.	171	
	Low	85	25.2	77.	162	
1914	High	90	29.2	90.3	175	
	Low	90	26.	77.	168	
1915	High	97	35.	92.	171	
	Low	90	18.	86.	165	
1916	High	112	34.6	89.	163	Inguinal lymph nodes palpable
	Low	92	26.4	85.	162	
1917	High	100	34.	91.	166	
	Low	87	25.5	80.	160	
1918	High	100	32.8	87.	161	
	Low	85	24.2	76.	160	
1919	High	98	43.7	95.	171	
	Low	87	25.	84.	162	
1920	High	100	41.	90.	170	
	Low	100	32.7	88.	167	
1921	High	100	31.	90.	160	
	Low	100	26.	88.	156	
1922	High	100	46.	89.	164	
	Low	95	22.7	84.	159	
1923	High	100	41.	97.	160	
	Low	95	26.	87.	157	

(*Chart continued on next page*)

Date		Hemoglobin (Sahli) %	White Blood Count 1000 cu. mm.	Lympho-cytes %	Weight Lbs.	
1924	High	100	38.4	95.	159	Angina
	Low	92	29.	90.	157	
1925	High	100	47.7	95.	156	
	Low	90	33.	86.	151	
1926	High	100	79.	96.	146	Diarrhea
	Low	74	22.1	90.	138	Roentgen-ray therapy
1927	High	100	44.	96.	143	
	Low	84	7.	68.	139	Roentgen-ray therapy
1928	High	94	26.7	90.	150	
	Low	83	10.	80.	144	Roentgen-ray therapy
1929	High	92	51.	96.	153	
	Low	78	29.	90.	150	Coronary thrombus
1930	High	100	24.1	93.	153	Roentgen-ray therapy
	Low	80	19.4	87.	150	Congestive heart failure
1931	High	91	35.	95.	167	
	Low	82	14.	89.	145	Roentgen-ray therapy
1932	High	92	57.7	98.	150	
	Low	70	25.	90.	149	Roentgen-ray therapy
1933	High	90	69.	97.	150	
	Low	79	38.	92.	149	
1934	High	90	112.	89.	142	
	Low	65	16.	90.	140	Roentgen-ray therapy
1935	High	85	22.2	96.	143	
	Low	72	12.4	86.	140	

blood examination showed a hemoglobin of 97 per cent and a red cell count of 4,775,000. He was then irradiated and anemia developed progressing to a maximum on July 15, at which time the hemoglobin was 74 per cent and the red cell count was 3,640,000. This anemia persisted throughout the rest of his life with remissions and exacerbations. At times, the blood picture was hyperchromic in nature and, for this reason, liver therapy was tried but without favorable response. Iron therapy was then instituted in the form of 60 grains of Blaud's mass a day which was always effective.

Diabetes

In February 1911, his glucose tolerance was determined by Dr. E. P. Joslin who pronounced him a mild diabetic. He was sugar-free upon a diet containing 170 grams of carbohydrates. He was instructed concerning the carbohydrate, protein and fat value of foods; he was also instructed to reduce in weight and to live on a diet which would not permit him to weigh over 170 pounds. Daily out-of-door exercise was advised and it was recommended that he take yearly winter and summer vacations. Thereafter, Mr. C. was an ideal patient. He watched his diet carefully and did not gain in weight. He walked six miles a day and played golf frequently. This exercise was continued until his cardiovascular system no longer permitted it. He usually rested after his noon-day meal. The vacations were taken as prescribed.

In fact, all through the remaining 25 years, he coöperated in every way. Because of his complete coöperation, his diabetes never presented any unusual problems. He is reported by Dr. Joslin, case No. 393.[3]

Cardiovascular Disease

As early as 1905, at the age of 48, the patient showed evidence of hypertensive heart disease. This condition slowly but gradually became more pronounced. The blood pressure became higher and the heart larger. In 1917, cardiac dullness extended to a point 1 cm. external to the left nipple. He had faithfully carried out his instructions as to daily exercise, walking and golfing when the weather permitted. In June 1924, he began to complain of dizziness. In September of that year, he had precordial pain after exercise. The pain radiated to the shoulders and down the arms. He was informed as to the cause of this pain and was instructed to recognize his limitations and to stay within them. This meant limiting his daily walks. He was furnished with a supply of nitroglycerin tablets (hypo), grains $\frac{1}{100}$, and was told to carry them with him at all times and to dissolve one under his tongue in the event of pain. Later, aminophyllin, grains 1½ after each meal, was prescribed. He did not worry about his condition and to the best of his ability attempted to carry out instructions. He had occasional attacks of pain. In August 1928, while in Canada, he had a severe attack of angina. He was seen by Dr. Robert Sterling Palmer of Boston who reported, "arteriosclerosis and hypertensive heart disease with anginal failure."

In November 1929, he had a very definite coronary thrombus and one month later, while still confined to his home, he had a second thrombus which nearly caused a fatal issue. Both of these attacks began with weakness, faintness, nausea and vomiting. The face was anxious, the skin was cold, moist and ashen gray in color. The radial pulse was scarcely perceptible early in the attacks. The blood pressure was lowered; the heart tones were diminished in intensity. No friction sound was heard over the precordium at any time; the thrombi evidently extended inwardly. (This probably accounts for the kidney infarcts which were never recognized clinically.) (See autopsy report.) Pain was not a factor in either attack. He recovered slowly under rest, morphine and aminophyllin. Thereafter, he was a weakened man. His activities were greatly reduced and he suffered little from angina.

Early in 1930, he began to show signs of congestive heart failure manifested by dyspnea and edema of the lower extremities. He was given digitalis, at first, two units a day and later, one-half unit a day. He lived solely because he recognized his limitations and stayed within them. On November 29, 1935, Mr. C. went to his office apparently feeling well for him. At 11:30 o'clock he had his luncheon and lay down on his couch to rest. A few minutes later his secretary found him dead.

A complete autopsy was performed by Dr. H. B. Davidson of the Pathology Department of the Ohio State University. The following is a summary of the findings:

1. Chronic lymphatic leukemia as evidenced by leukemic changes in lymph nodes, spleen, bone marrow, lungs, pericardium, liver, bladder and prostate.
2. Generalized arteriosclerosis, and generalized arteriolar sclerosis.
3. Cardiac hypertrophy and dilatation. Myocardial degeneration, fatty infiltration, and fibrous replacement.
4. Thrombosis of right coronary artery. Complete obliteration of the anterior descending branch of the left coronary artery below a point 2 cm. from its origin.
5. Senile arteriosclerotic nephritis.
6. Healed infarcts of each kidney.
7. Medullary hyperplasia of the adrenals.
8. Benign prostatic enlargement.

9. Atrophy and fatty infiltration of pancreas.
10. Healed childhood tuberculosis.
11. Bronchiectasis.

COMMENT

First, the duration of the leukemia after discovery was 25 years, which the author believes to be the longest survival period recorded.

Second, the duration of the leukemia prior to its discovery in 1911 is unknown because of no record of blood examination before that date. It should be noted, however, that besides the diarrhea, the only symptoms of the leukemia that the patient presented were a sense of fullness in the epigastrium and acid eructations and he complained of these symptoms when he first consulted the author in 1905.

Third, it is the writer's opinion that the patient lived through all of these years largely because of his complete coöperation with his physicians.

Fourth, the diagnosis of cardiovascular disease, made as early as 1911 by the late Dr. John Musser, is worthy of comment.

Fifth, the response of the diarrhea to the irradiation was quite remarkable.

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PAROXYSMAL HEMOGLOBINURIA WITH REPORT OF A CASE*

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THE term "hemoglobinuria" is used to designate the excretion of blood pigment in the urine with total absence of red blood cells, or with only a relatively small number that cannot be considered sufficient to explain the altered, bloody or dark blood like, appearance of the specimen.

This phenomenon is observed: (1) when hemoglobin in sufficient quantity is injected into the blood stream; (2) after procedures resulting in solution of the red blood cells, such as transfusion of blood, or the injection intravenously of incompatible blood serum of another species, of distilled water, glycerine, oil or many other chemical substances; (3) after certain organic or inorganic poisons have made their way into the blood stream in sufficient quantities, whether from the intestinal tract, or through the skin and mucous membranes, following either ingestion, inunction or injection. The list of such poisons includes a number of substances used for therapeutic purposes, e.g., chlorates,

* Received for publication January 18, 1935.

phenol, glycerin, tincture of iodine, sulfuric acid, hydrochloric acid, quinine, etc.; (4) after extensive burns, and in consequence of certain severe infections, such as scarlet fever, erysipelas, typhoid fever, pernicious malaria; (5) in certain severe hemolytic anemias when hemolysis is unusually rapid and extensive, for example in sickle cell anemia and in Lederers anemia; (6) lastly, in *periodic* or *paroxysmal* (intermittent) *hemoglobinuria,* a peculiar chronic affection in which hemoglobin appears in the urine at intervals accompanied by a characteristic clinical syndrome.

The development of our present knowledge of this rare condition, paroxysmal hemoglobinuria, has been gradual. A number of men have contributed descriptions of features of the syndrome which are now considered essential to its recognition. Dressler described a patient with intermittent bloody urine in 1854 and noted that the color was due to hemoglobin in solution and not to whole blood. Pavy in 1866 differentiated hemoglobinuria of the paroxysmal type from that occurring in connection with malaria. Gull in the same year described the effect of chilling in bringing on an attack. Rosenbach (1880) showed that by placing the patient's feet in ice water an attack could be artificially produced. Kussner (1879) by observing the blood serum during an attack demonstrated that hemoglobinemia accompanied the hemoglobinuria. Murri (1880) called attention to the association of paroxysmal hemoglobinuria with syphilis, evidences of which he found present in nearly 50 per cent of the reported cases. In 1881 Ehrlich showed that hemoglobinemia was produced locally at the site of chilling; the immersion in ice water of a finger about the base of which a ligature has been placed led to hemolysis of the blood within the vessels of this finger. He felt that a hemolysin was produced by the chilled tissues. In 1904 the mechanism of the disease was further elucidated by Donath and Landsteiner whose experiments indicated that in patients with this disease an auto-hemolysin is present which acts in two phases: (1) union of the lysin with the red corpuscles at low temperatures, and (2) lysis of the red corpuscles so attacked, when the temperature again rose to normal. Complement is necessary for the reaction. Since that time numerous workers have studied this mechanism and added to our knowledge of factors which qualify the behavior of the autolysin; the essential observations, however, have all been confirmed.

Study of the case reports since the introduction of the Wassermann test has shown that syphilis is present in well over 90 per cent of cases which exhibit the other criteria of paroxysmal hemoglobinuria. Congenital syphilitics are more prone to the condition than cases of acquired syphilis. Sufficient evidence has now been gathered to prove that effective antiluetic therapy will usually result in disappearance of the attacks of hemoglobinuria. It has become apparent that the degree of chilling necessary to initiate an attack is not the same in all cases. Exertion has also been shown to precipitate hemolysis in some cases of the disease, and in certain instances it is possible that acute emotional disturbances may have a similar effect. Cases of paroxysmal hemoglobinuria have now been described in most countries and races of the world and at all ages. It is a very rare condition as shown by its low incidence even in large hospital clinics. In its milder forms it is probably often overlooked or misinterpreted.

Paroxysmal hemoglobinuria is essentially a chronic condition with episodic acute attacks of varying severity. In the interval between attacks the patient's

state of health will depend upon the nature and activity of the underlying syphilitic disease and upon the degree of depletion and anemia induced by the preceding attacks of hemolysis. The incidence of the attacks is greater in cold weather. Exposure to cold and wetting of the hands and feet in cold water are the most important precipitating factors.

The duration of the attack is from half an hour up to three or more hours. It is frequently ushered in by a chill, which is followed by a fever rising at times to 104° F. There is often a dragging pain in the back, running down into the thighs, pallor of the skin, and later cyanotic discoloration of the finger tips, toes, and ears. Lassitude, a tendency to yawning, oppression, nausea, pain in the hypochondrium, and occasionally neuralgic pains in the extremities have been observed. The fever is followed by sweating and subsidence of the subjective symptoms.

A macular hyperemia with urticarial wheals may be seen during the attack. Pargnes reported a case in which urticaria could be produced by cooling the hands, the wheals, of a peculiar reddish color, lasting for two hours or more.

Examination of the patient during convalescence from an attack may show evidence of slight enlargement of the spleen and liver, and slight icteric discoloration of the skin and mucous membranes.

The urine during the attack appears bloody or dark reddish brown. On spectroscopic examination it shows the presence of oxyhemoglobin, or methemoglobin and occasionally of other blood pigments. On microscopic examination amorphous blood pigments in granules or irregular masses, or in the form of casts are found but few if any red blood corpuscles. In addition, the urinary sediment often contains hyalin and granular casts, renal epithelium, and cells, the nuclei of which are also stained red. The urine always contains albumin and often bile pigment, but bile acids are absent. As the attack subsides the urine gradually becomes paler, until it resumes its normal color, but albumin remains present for a few days. The appearance of albumin may precede the discoloration. The excretion of hemoglobin is dependent upon the degree of hemoglobinemia and the kidney threshold for hemoglobin, factors which vary with the individual and with the particular attack.

It has been shown that following the attack the hemoglobin in the blood plasma rapidly disappears with a corresponding rise in blood bilirubin and somewhat later an excess excretion of bile pigments in the bile.

The effect upon the blood picture of the attack of hemolysis is of some interest. There is initially a leukopenia which is followed in several hours by a well-marked leukocytosis. Increased viscosity and lengthened coagulation time may accompany the period of leukopenia (Widal). The effect upon the red blood cell count will depend upon the severity of the attack. In some cases falls of over one million cells per cu. mm. have been observed. Rapid regeneration is the rule but in the cold season when attacks are frequent there is often a moderately severe secondary anemia.

The diagnosis of paroxysmal hemoglobinuria usually starts with the demonstration that the dark or bloody urine which has been noted by the patient owes its color to hemoglobin in solution and not to whole red blood cells. To establish this point a perfectly fresh specimen must be examined, the absence or rarity of erythrocytes proved, and the nature of the pigment spectroscopically

determined. If intermittent hemoglobinuria is present the other features of the syndrome, hemoglobinemia, the induction of attacks by chilling the feet in cold water, the presence of the Donath-Landsteiner phenomenon, and the discovery of a history or of lesions or of serological tests indicative of syphilis, will serve to complete the diagnosis.

Case Report

W. B. B., a white male, 30 years of age, by occupation a spinner of artificial silk, complained of recent attacks during which he passed bloody urine. He had been married for six years; his wife was living and apparently well. There had been one pregnancy which resulted in a still birth at full term. His family history was negative. He stated that prior to the recent illness his general health had been excellent. At the age of 18 he had had an attack of "three-day measles," at 19 epidemic parotitis and at 13 influenza. He at first denied any history of venereal disease but later let it be known that nine years before a positive Wassermann reaction had been found and that he had then received six injections of an arsenical at weekly intervals.

There had been no cardiorespiratory symptoms except for slight dyspnea on climbing a flight of stairs. His appetite, digestion and bowel function were normal. There was no history of icterus. There had been an occasional "stitch in the right side" while working (his occupation necessitating a half twist of the body). There had been no urinary symptoms prior to the recent illness. No joint symptoms, no disturbances in locomotion, nor had any abnormalities of the special senses been noted.

There was no history of bleeding, no epistaxis, hemoptysis, hematemesis or melena. The patient stated that he smoked moderately. He had not used alcoholic beverages for 12 years. There was no history of exposure to chemicals, nor of drug addiction nor of prolonged medication of any sort.

About November 1, 1933, the patient, having been exposed to cold weather for about three hours while hunting, became chilled and began to "quiver"; at once he went to a house close by, where his temperature was taken and found to be 104° F. He stood before an open fire in this house for approximately three-quarters of an hour, feeling during this time perfectly normal. The first urine voided, about one hour later, was slightly tinted blood color; a second specimen one hour afterward was bright red, and the third, after about six hours, was clear. There were no abdominal cramps, pains, or discomfort; no icterus, pallor, flushing of the face, dizziness, tinnitus, headaches, nausea, vomiting, disturbances of vision, sweating or petechiae.

Following this initial attack, in the winter of 1933–34 there occurred five similar attacks. During the summer of 1934 no attacks were noted but about November 8, 1934, an attack again occurred. On this occasion he had been working on an automobile for about two hours on a cold day in a small garage without a stove. During the prodromal stage he felt that he was able to predict that the "urine would be bloody" because of his previous experiences; the feet and then the hands became rapidly and exceedingly cold, followed by a coarse generalized tremor and "nervousness." Upon entering the house to get warm, he noticed a fairly severe tinnitus and a feeling as if his head were swelling. The hemoglobinuria followed the same course as in previous seizures. Following this he came in for diagnosis.

Physical examination reveals a well nourished adult male, approximately 30 years of age, with slightly pale lips, but apparently in good health. Skin of normal color and texture. Head: of normal contour, without softening, exostosis, or loss of hair. Tongue protrudes in the midline, without tremor; facial and masseter muscles are intact. Eyes: pupils round and equal, react to light and in accommodation; extra ocular movements normal; no nystagmus. No icterus. Ears: hearing normal; slight

scarring of the right tympanic membrane. Nose: symmetrical without discharge or deviation or perforation of the septum. Mouth: no ulceration or scarring. Tongue normal. Upper teeth all extracted, others in good repair. Neck: symmetrical, without retraction, muscle spasm, deviation or tug of trachea. Chest: symmetrical, with normal respiratory excursion; lung fields are normal as to voice sounds, breath sounds, tactile fremitus, and percussion. Heart: apex beat in the fifth interspace 8.5 cm. to the left of the mid-sternal line, regular in rate and rhythm, without murmurs. Blood pressure 128 systolic and 80 diastolic. Abdomen: symmetrical; panniculus at the level of the thorax. No muscle spasm, abnormal masses, or point tenderness. Costo-vertebral angle tenderness is absent. Genitalia: no abnormal findings. Extremities: symmetrical, without limitation of motion, scars, or tremors. Tendon reflexes present, equal and active. Babinski test causes plantar flexion of the great toes. Romberg is negative.

*Laboratory Examinations.** Blood: Hemoglobin 75 per cent; red blood cells 5.09 millions; white blood cells 8,650; smear normal. Wassermann and Kahn tests were positive (4 plus); colloidal gold 555554310000.

The Landsteiner phenomenon showed unmistakable hemolysis. A few cubic centimeters of the patient's blood were put in a test tube with a little citrate solution, and a normal control used. Both specimens were cooled to about 5° C. for about 10 minutes and then warmed to 37° C. When the cells had settled out, the serum of the normal blood was a straw color and that of the patient's blood a wine color. Under the microscope the cells of the control were normal, while about one-third of those of the abnormal specimen were somewhat elongated with very slightly irregular outlines. Urine: A specimen taken when an attack was not imminent had a specific gravity of 1.012, and tests for albumin and sugar were negative. During an attack the benzidine reaction was strongly positive, and the red cells averaged less than two per low power field in a centrifuged specimen.

The Wassermann reaction on the blood of the patient's wife was strongly positive.

Course. The patient was promptly placed on anti-syphilitic treatment. He received his first intravenous arsphenamine on December 21, 1934. Since that date there has been no recurrence of paroxysmal hemoglobinuria. During the ensuing 10 months the patient received 12 intravenous injections of neoarsphenamine, 12 intramuscular injections of bismarsen and interval oral administration of protoiodide of mercury. In late 1935 he was noted to be developing a noticeable increase in mental dullness and apathy, a forgetfulness in relation to misplaced articles of dress and ordinary use. His gait was uneven. A slight inequality of the pupils was found with diminished reaction to light. An observable slurring of test sentences was noted and an increase, bilateral and equal, of the biceps and knee reflexes. The spinal fluid Wassermann test was strongly positive. A diagnosis of paresis was made. Active treatment with mercury and arsphenamines was continued but without benefit. A course of hyperpyrexia of six weeks' duration had likewise no definite helpful effect.

Summary

A case of paroxysmal hemoglobinuria is reported, occurring in a white male 30 years of age. Treatment of the patient's syphilitic infection led to prompt disappearance of the attacks of hemoglobinuria but the syphilitic infection progressed and outspoken general paresis appeared.

* We are indebted to Dr. Ivan H. Smith for the laboratory findings.

PERICARDITIS WITH EFFUSION COMPLICATING TULAREMIA *

By D. D. Stofer, A.B., M.D., F.A.C.P., *Kansas City, Missouri*

Because of the fact that tularemia is somewhat rare, its complications are not fully known. The purpose of this paper is to report the recovery of a case of tularemia in which pericarditis with effusion occurred as a complication. A search of the literature in the Surgeon General's Library and other available sources reveals but one other case of this kind. Pessin [1] (1936) reported a case of pericarditis with effusion complicating tularemia, which was diagnosed a few days before death of the patient and verified by autopsy findings. The clinical findings in his case as well as in this one were unquestionable as to the existence of a pericarditis with effusion.

Case Report

The patient was a white woman, 29 years of age, married. Her husband and two children were living and well.

On November 8, 1936, her husband returned home with three rabbits which he had shot on a farm seven miles south of Belton, Missouri. She cleaned the rabbits that night. On the following Sunday, November 15, 1936, she noticed a small raised red area on the dorsum of her right index finger just back of the nail which she said itched considerably. The area became infected in appearance and began to ulcerate. Lymphatic glands in the epitrochlear region and axilla of the right arm commenced to swell markedly and become very painful. A day or so later she noticed a peculiar choky sensation in her throat, accompanied by nausea, profuse sweating at times, chills, fever and pleurisy-like pains in the left chest.

Physical Examination: At the first visit November 15, 1936, the patient's temperature was 103.2° F. and her pulse 116. She appeared to be in a very excited and uncomfortable state, with difficulty in breathing because of the pleurisy-like pains in her left chest and very severe pains in the index finger of the right hand and up the arm into the axilla. Just back of the base of the finger nail of the right index finger there was an ulcerated area about 1 cm. in diameter with lipping of the edges. A large swollen and tender bunch of glands were evident in the epitrochlear region extending about one-third of the way up the arm from the elbow to the axilla. A group of swollen glands was also found in the axilla.

On further examination the following findings were noted: The tongue was furrowed, red and sore; there were a few small ulcerated areas along its edges. The examination of the heart was negative except for its rapid rate. A few moist râles were heard at the base of the left lung but there was no dullness to percussion. A very slight friction rub was present at the left base. The abdomen was slightly distended.

This clinical picture remained about the same, the temperature each day going as high as 102 to 103.8° F. until November 29 when the patient's left chest became definitely dull to percussion over the entire lung area, some bronchial breathing appeared and more râles were evident. Hospitalization was deemed advisable.

The patient was admitted to St. Luke's Hospital on November 30. The tem-

* Received for publication August 2, 1937.

perature and pulse chart during her stay at the hospital from November 30, 1936 to February 7, 1937 is shown in figure 1.

The results of laboratory examinations made during the patient's stay in the hospital were as follows:

The agglutination test for *B. tularense* on the fifteenth day was negative; on the seventeenth day it was reported positive in all dilutions up to 1:640; and on the nineteenth day it was positive in dilutions up to 1:1280. A blood culture taken on December 2 was negative after 72 hours. On admission the white blood cell count was 11,800. Later counts up to January 30 varied between 8,300 and 12,600. The red blood cell count was 4,160,000 and the hemoglobin 89 per cent on admission; later counts showed no significant variation.

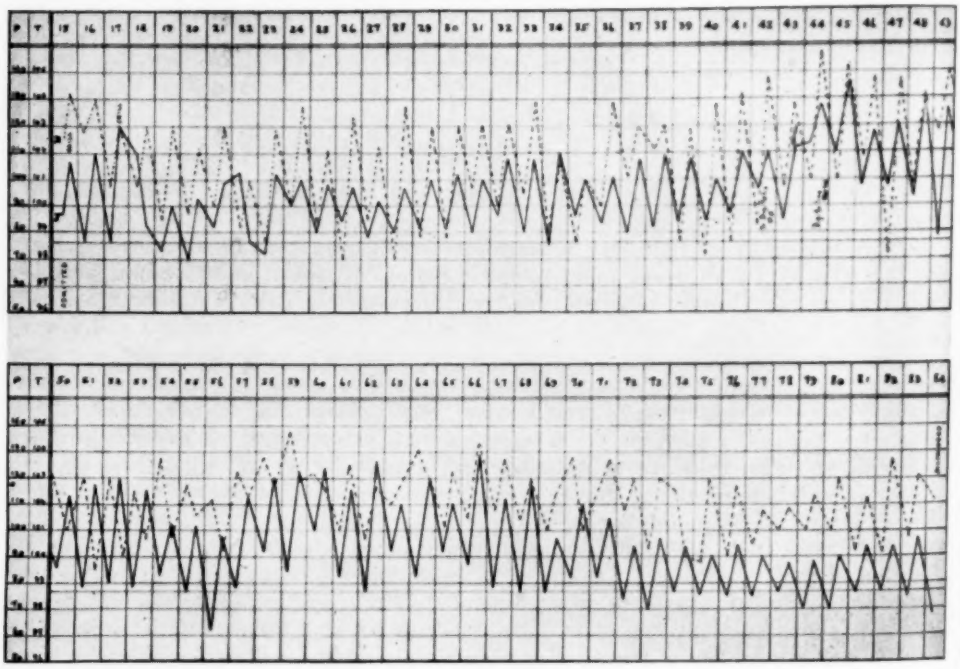

FIG. 1. Temperature chart during the patient's stay in the hospital.

The Wassermann and Kline tests were negative. Urinalysis on admission showed a faint trace of albumin and 10–12 red blood cells per high power field in the sediment.

On December 2, 1936 a roentgen-ray of her chest was taken (figure 2) which showed a definite pneumonitis of the left lung with some fluid at the left base. The heart shadow was normal in size and contour.

On December 6, 1936 there appeared on the right forefinger, hand and arm a large number of pustules which persisted for approximately two weeks. From the above date on to December 27, 1936 she complained of severe pain in her arm, chest, right side of neck and at times in the right side of her abdomen, accompanied by nausea and vomiting. No definite tenderness could be found over her appendix. A pelvic examination was negative.

December 27, 1936 she began to complain of tightness in her throat and of some

difficulty in breathing. A careful daily examination of the heart had disclosed nothing of importance until the above date when a slight increase of the area of cardiac dullness was noted. On December 28, 1936 the area of cardiac dullness was larger and by the following day was markedly enlarged. The heart sounds became very distant. The apex beat could not be felt.

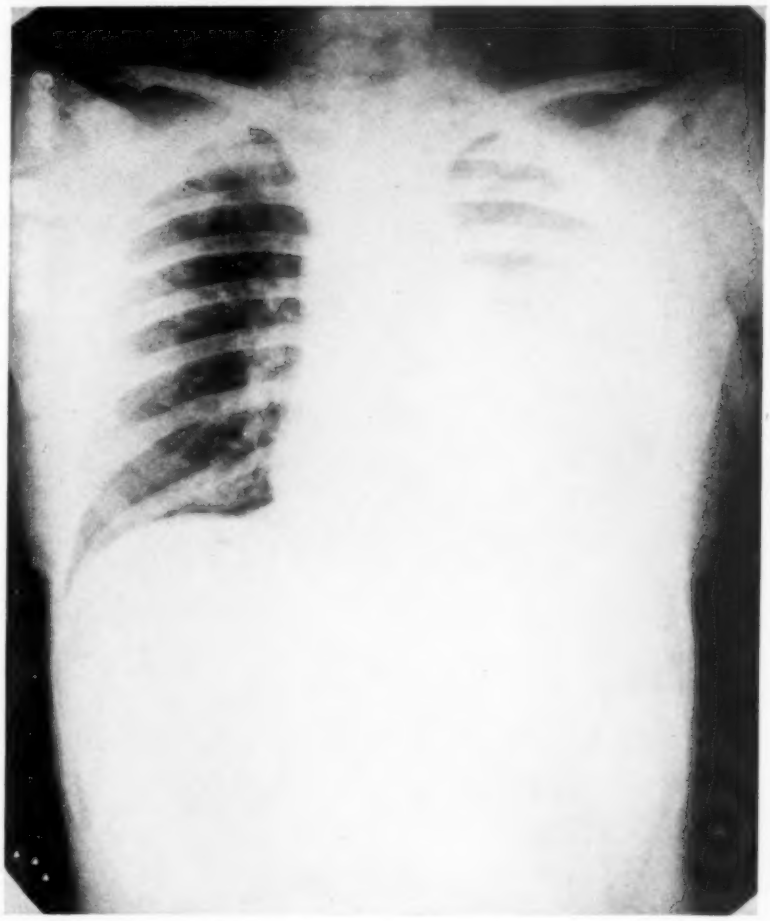

FIG. 2. Roentgenogram during the active stage of the left pneumonitis and pleural effusion and before the development of clinical evidence of pericardial effusion (December 2, 1936).

A roentgen-ray of the chest (figure 3) on December 30 showed the pneumonic process in the left lung greatly improved but the heart shadow area enlarged from its previous greatest transverse diameter of 15.5 cm. to 22 cm. There was a marked variation of density over the heart shadow area, particularly at the outer edges (not shown in the photographs as plainly as in the original film) suggesting a pericarditis with effusion. Another roentgen-ray on December 31 showed identical findings.

No pericardial friction rub was found until January 3, 1937 when it was very

pronounced. The rapid filling of the pericardial cavity probably accounted for the absence of the friction rub at first. The to and fro friction rub remained very constant day after day until January 12, 1937. On several days between January 3 and January 12 she was subject to sudden stabbing pains in her chest. On January 11 a definite and distinct pleural friction rub at the right base was noted which persisted for two days, and was intermittently observed thereafter until January 30, 1937 when all signs through her chest began rapidly to disappear. At no time during

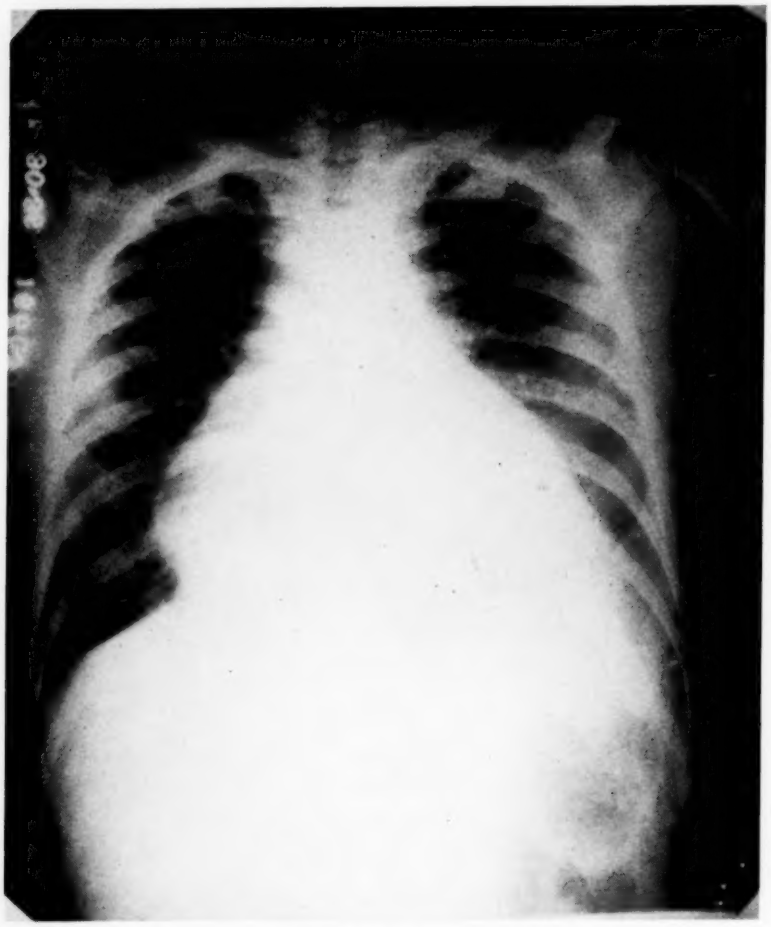

FIG. 3. Roentgenogram showing pericardial effusion. Marked clearing of the left chest has occurred (December 30, 1936).

the course of the pericarditis with effusion was it deemed either necessary or advisable to tap the pericardial sac. The embarrassment of respirations experienced was at times considerable but never unbearable.

A roentgen-ray of the chest on January 15 showed some decrease in the heart shadow area. The lung fields appeared entirely clear at this time.

An electrocardiogram was taken on January 12 (figure 4). In the conventional

three leads: P.R.I.—0.15 sec.; T_1 plateau type with slight convexity upward of RT_1 segment; T_2 and T_3 are diphasic; QT—0.21. In the anterior chest leads (R.A. to front and L.A. to back): T_4 is diphasic and of low voltage; T_5 is diphasic and of low voltage but more upright than T_4; Q_5 is smaller than normal.

Impression: Impairment of coronary circulation leading to poor myocardial nutrition.

By February 3, 1937 very definite clinical improvement was evident. A roentgen-ray of the chest at this time (figure 5) showed a marked diminution of the area of the cardiac shadow. The lung fields were clear. The patient was dismissed from the hospital February 7, 1937 to go to her family's farm to recuperate. Upon dismissal she still had some enlargement and hardness of her epitrochlear glands. At

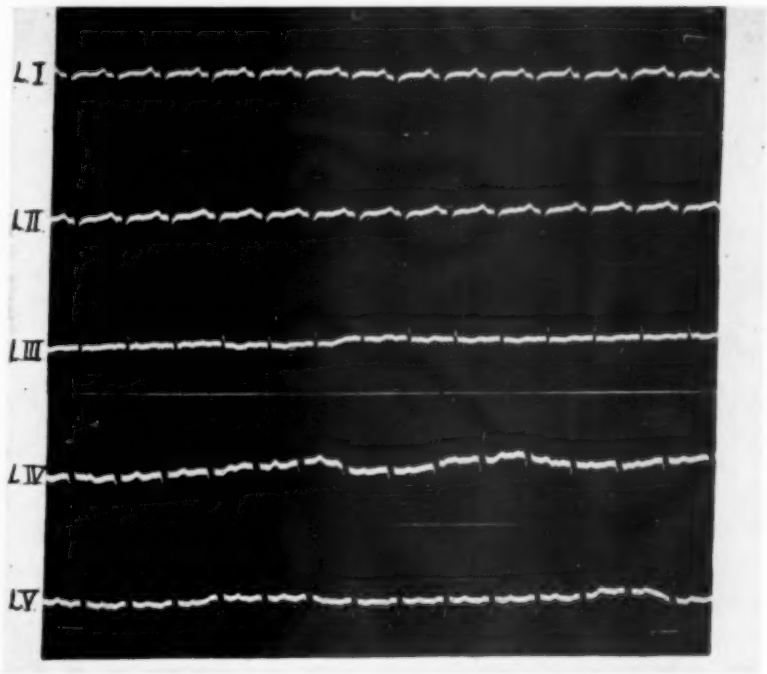

FIG. 4. Electrocardiogram (January 12, 1937).

no time during the course of the disease did the glands suppurate enough to warrant incision and drainage or aspiration. The multiple pustules which had appeared during the third and fourth weeks of the disease were incised and drained to relieve pain.

Although some writers on the subject of tularemia report that the initial lesion disappears in a week or two after its inception it was observed in this case that the initial lesion on the finger lasted for over a month. The secondary pustules which developed on the arm about two weeks after the initial lesion appeared did not dry up until the same time that the primary focus disappeared.

The total duration of the illness in this case was 114 days. Following discharge the patient made a complete recovery and is at present well and leading a normal life.

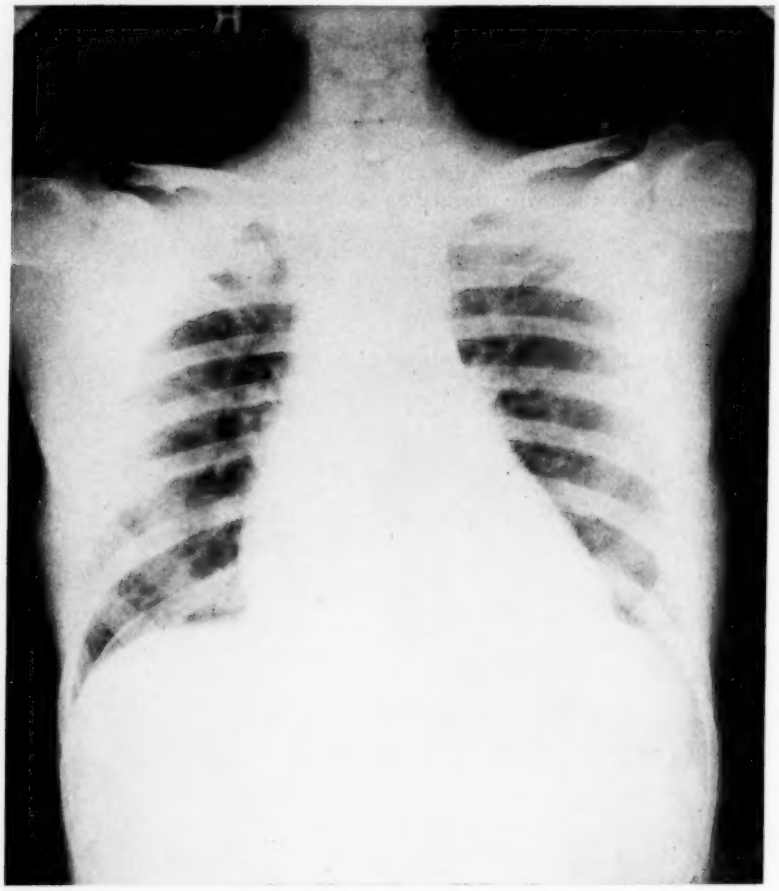

FIG. 5. Roentgenogram showing reduction in area of heart shadow by February 3, 1937.

SUMMARY

A case of tularemia of the ulcero-glandular type is reported in which pericarditis with effusion appeared as a complication. The patient made a complete recovery.

REFERENCE

1. PESSIN, S. B.: Tularemic pneumonia, pericarditis and ulcerative stomatitis, Arch. Int. Med., 1936, lvii, 1125.

EDITORIAL

ERYTHROBLASTOSIS

The erythroblast is an immature form of red blood cell usually considered to be the next in sequence of development after the megaloblast. It contains a large nucleus and according to certain authors may contain nucleoli. According to others it never contains nucleoli and is incapable of mitotic division. It is evident that this is a matter of definition. The cytoplasm is basophilic and contains little or no hemoglobin. The diameter is variously given as from 8 micra to 25 micra. The smaller forms are certainly the more usual.

Erythroblasts are normally observed in the blood of new born infants during the first five days of life but thereafter they are normally found only in the red marrow where they constitute up to 5 per cent of the cells.

In anemias with rapid cell regeneration as after certain infections and in myelogenous leukemia, erythroblasts may appear temporarily in the blood and the younger the patient the more likely this is to occur. There are in addition, however, certain more or less specific types of anemia in infancy and childhood in which a very considerable number of such nucleated red cells are seen and it is to these that the term erythroblastic anemia has been applied. The specific features common to these anemias in addition to erythroblastemia are: (1) the extramedullary proliferation of hematopoietic tissue and associated enlargement of the liver and spleen; (2) excessive blood destruction with varying grades of associated icterus, anemia and edema; (3) familial occurrence. The different types in this group are distinguished by their age of incidence and by their individual clinical features which often are very striking. Sufficient cases completely studied in life and as to their pathologic histology are not yet available to warrant any final classification. There is especially a lack of sufficient data for any final opinion on the hereditary factors in certain types of cases. Nevertheless a tentative description of the group is of interest.

Universal edema of the fetus, or congenital hydrops has long been known. The major portion of the course of this disease is run in utero and it results in the production of a non-viable infant or of a still birth. At birth the extreme whiteness of the infant suggests the severe anemia present. The vernix caseosa may be quite yellow. The patient is dropsical either in toto or as to the extremities. The placenta is edematous and enlarged often to several times its normal size. The enlargement of the spleen and liver are very marked. There is free fluid usually in all the body cavities.

If the child is living at birth respiration is usually irregular and gasping. The heart sounds are accompanied by hemic murmurs. The blood count shows a very severe anemia, frequently less than one million red blood cells

per cubic millimeter being recorded. There are numerous erythroblasts and normoblasts the percentage of such nucleated forms often reaching 40 to 60 per cent of the total red cells. Immature white cells are likewise present.

The histological study of the organs shows striking increase in the erythropoietic activity not only in the bone marrow but in diffusely scattered foci in the spleen, liver, lymph glands, kidneys and numerous other glandular structures. Such foci are also present in the edematous placenta. Hellman and Hertig [1] believe that the pathologic picture of the large smooth edematous placenta of this condition is specific for the disease.

It has recently been shown that fetal hydrops can be diagnosed by the roentgen-ray in utero.[2] The edematous thickening of the scalp shows as a dark corona around the infant's skull. There is also thickening and increased density of the soft parts generally. Since the condition is incompatible with life and since it is familial, it is probably advisable to take roentgenograms of pregnant mothers who have previously given birth to erythroblastotic children. Such roentgen-rays are especially apt to show positive findings in the last two months of the pregnancy.

A recent study [3] of the mode of inheritance of fetal hydrops has shown that in those families in which one or more cases of this condition have occurred there is also a high incidence of miscarriages and still births. A more careful pathological study of these products of conception might show that many were earlier forms of erythroblastosis. It seems probable that the occurrence of fetal hydrops in families is due to a dominant mutation.

Icterus gravis of the new born is another condition characterized by the presence of erythroblastic anemia, extramedullary hematopoiesis with enlargement of the liver and spleen and by a well marked tendency to familial incidence.[4, 5] At birth the vernix caseosa has usually been found to be of a golden yellow color. The infant is slightly icteric, the spleen and liver are already large and there are not infrequently small petechial hemorrhages. The jaundice tends to increase rapidly, the bleeding tendency becomes more marked with oozing of blood from the mouth, nose and in the urine and stools, and, unless relieved by treatment, death will usually occur within the first week. These cases show a severe anemia, the count frequently being below two million. There is a high percentage of nucleated red cells. The leukocytes are increased to around 25,000 in the average case, with evidences of marked immaturity among the myeloid cells. It has been noted

[1] HELLMAN, L. M., and HERTIG, A. T.: The pathological changes in the placenta associated with erythroblastosis of the fetus, Am. Jr. Path., 1938, ix, no. 1.

[2] HELLMAN, L. M., and IRVING, F. C.: The X-ray diagnosis of erythroblastosis, Surg., Gynec. and Obst., 1938, lxvii, 296–299.

[3] MACKLIN, M. T.: Erythroblastosis foetalis, a study of its mode of inheritance, Am. Jr. Dis. Children, 1937, li, 1245–1267.

[4] CLIFFORD, S. H., and HERTIG, A. T.: Erythroblastosis of the new born, New England Jr. Med., 1932, ccvii, 105–113.

[5] DIAMOND, L. K., BLACKFAN, K. D., and BATY, J. M.: Erythroblastosis fetalis and its association with universal edema of the fetus, icterus gravis neonatorum and anemia of the new born, Jr. Pediat., 1932, i, 269–309.

in this condition that the red count may show a very rapid fall within a period of a relatively few hours, a phenomenon recalling the hemolytic crises observed in two other familial blood diseases, sickle cell anemia and congenital hemolytic jaundice. There may be slight edema present in the subcutaneous tissues of these cases. Transfusions appear to benefit many cases. Those patients in this group who survive frequently show severe grades of anemia for a long time after the icterus has disappeared. In some instances there has been evidence of persistent damage to the central nervous system. The later history of these cases deserves more intensive study.

The postmortem examination of cases of icterus gravis shows evidence of unusually active and widespread erythropoiesis in liver, spleen, kidneys and other organs. It is not perhaps usually of as embryonic a type as that seen in fetal hydrops. The enlarged liver shows vacuolization of many liver cells; bile casts in the bile ducts; hemosiderin pigment in the Kupffer cells. In some cases, the hematopoietic islands compress the liver columns, destroying liver cells. The nuclear structures of the brain may show intense icteric pigmentation. This condition described as "Kernicterus" is thought to be the cause of the persistent neurological defects.

Macklin in studying the inheritance of icterus gravis as exemplified in the published cases, found that in the families in which it occurs, a little over 50 per cent of the children are affected. This suggests that it is due to a dominant mutation. It is of interest that in a number of instances infants showing fetal hydrops and others showing icterus gravis have been born in the same family.

It is less clear whether the condition known as anemia of the new born, or hemolytic anemia of the new born, should be classed as another example of erythroblastosis. In the cases so designated neither icterus nor hydrops are prominent, though traces of either may be seen. A severe anemia is observed within a few days or weeks after birth. This anemia is usually accompanied by moderate evidences of immaturity among the red cells of the peripheral blood, but a true erythroblastemia is not a characteristic feature. Similarly, extramedullary hematopoiesis is not prominent in the pathological examinations of such cases. There is some evidence that anemia of the new born may occur in the same families in which fetal hydrops or icterus gravis have been observed.

A very interesting type of erythroblastosis is that first described by Cooley in Detroit in 1925 among American born children of Greek, Syrian or Italian parentage. Cooley and his colleagues in a number of papers define the essential features of this type of anemia now commonly known by his name. The onset of the condition is in infancy or in early childhood. There is a moderately severe anemia, with, as a rule, a low color index. The number of nucleated red cells is greatly increased, often to 5,000 per cmm. The majority of these are normoblasts, but 5 to 10 per cent may be erythroblasts. The spleen and liver are greatly enlarged, but the evidences of extramedullary hematopoiesis were found to be relatively scant in the

autopsied cases. Evidence of chronic hemolysis in these cases exists in the form of a yellowish, muddy, skin pigmentation and an excess of urobilin in the urine. There is usually a positive indirect Van den Bergh reaction and an increased icterus index. There is a distinct familial character to the disease, as well as a racial distribution. The striking feature of this chronic familial type of anemia is that it exhibits bone changes similar to those seen in certain cases of sickle cell anemia and familial hemolytic jaundice. These bone alterations consist of irregular lacunar areas of osteoporosis, most commonly seen in the pelvic bones, femurs, and the metatarsals and metacarpals. In addition, there are striking vertical striations in the enlarged diploë of the skull. These changes may also affect the malar bones. The color of the skin and the changes in the contour of the face join in giving to these patients a rather marked mongoloid appearance. The course of Cooley's anemia is usually fatal, death occurring before puberty.

Until very recently the total number of cases reported of this disease did not exceed sixty. The great majority had been observed in the United States. An important publication has just appeared, based upon the studies of Caminopetros[6] in Greece. The author has observed 36 cases in the course of the last three years. Since certain of these were refugees from Asia Minor, he feels that the disease deserves investigation among all the peoples of the Near East. Caminopetros believes that a definitely increased resistance of the red blood cell to salt solutions is an essential feature in Cooley's anemia. Moreover, he feels that he has shown that this characteristic of the disease is frequently present in members of the families of patients who do not themselves show any manifest anemia. He is inclined to feel, that since the condition may be transmitted by apparently normal adults, there is a real possibility that the disease may increase in frequency. He points out that radiologic examinations of the recovered skulls of members of the vanished Maya Indian race have shown severe osteoporotic lesions quite similar to those seen in the erythroblastic anemia described by Cooley. This raises the question, he feels, as to whether a familial anemia fatal before puberty may not endanger the existence of a race.

In this brief summary the many diagnostic difficulties which arise in connection with the separation of the above described types from conditions nearly resembling them have not been discussed. Much further study of these types and of closely similar conditions will be necessary before the true significance of the resemblances between the different types of erythroblastosis can be finally determined.

[6] CAMINOPETROS, J.: L'anémie érythroblastique infantile, Ann. d. Méd., 1938, xliii, 27–61 and 104–125.

REVIEWS

How Ancient Healing Governs Modern Therapeutics. By KLEANTHES A. LIGEROS, M.D., Ph.D. Illustrated. xx + 523 pages. Index. G. P. Putnam's Sons, New York and London. 1937. Price, $10.00.

Dr. Ligeros apparently has taken up a twofold task. The first is to show that medicine has advanced very slowly, and in some respects not at all, since the days of ancient Greece. His second, and major thesis, is to demonstrate that "Chiropractic" or "rachiotherapy" was an important branch of treatment in the Hippocratic school, and is now, in spite of the reluctance of the medical profession to approve it, coming into its own as a modern therapeutic method.

Several quotations might be cited. On page 48: "Among the systems to be thus reborn is rachiopathy and rachiotherapy, rediscovered in America forty years ago as chiropractic, and advanced since that time as a new science and art. Its efficacy and scientific value have been verified and confirmed by modern research as well as by the findings of the ancient Greeks. . . ." Page 81: "Taking into consideration the conflicting and chaotic condition of today and the untold and endless theories propagated so far—which change before they can be reasonably discussed—and the advances in medicine relative to the cause of disease, it is not difficult to prove that perhaps the ancients were better off and nearer the truth than we are." Page 82: "Evidently the new theories of the cause of disease (such as the germ theory of Pasteur) have not yet solved the problem which keeps the medical world divided and disdainful. Undoubtedly, the germ theory of the cause of disease still remains a source of academic discussion and a question to be answered. . . ." "In the sphere of actual technique, the modern physician is left astonished and dumbfounded, not being able to equal or meet his predecessor half way." Page 93: "Sanitation, hygiene, and dietetics were developed so adequately from the time of Hippocrates that even today science has not added anything of great importance to them, particularly to the last named." Many more such statements could be quoted, but these passages give a fairly accurate picture of the general tone of the book.

Much space is devoted to the Homeric period. Most of this is irrelevant, though interesting. In describing the knowledge of pharmacy possessed by the Homeric Greeks, one author states that Circe, the enchantress, knew a number of effective drugs with which she transformed Ulysses' crew into swine; the modern pharmacologist has certainly not succeeded in performing this feat! Dr. Ligeros makes no distinction between legend and historic fact, and, if the reader's only acquaintance with Greek culture was through the present volume, his opinion would certainly be distorted.

Two appendices are included. One is titled "Chirurgy in Ancient and Modern Times," and the other "An Historical Acknowledgment on the Discovery of Modern Rachiotherapeutics." The second appendix, as suggested by the title, takes up the history of modern "Chiropractic." D. D. Palmer, the founder, is quoted extensively from his book "The Science, Art and Philosophy of Chiropractic." The first appendix, also, is largely devoted to Chiropractic methods, and opinions of Goldthwait, Still, and others are quoted as approving the Chiropractic method. The author seems unable to distinguish between true disease of the spine, and the so-called subluxations that, according to the "Chiropractic School" are responsible for all human ills.

This book is not recommended for the physician or medical student, but it should certainly be in every Chiropractic's library.

T. N. C.

Artificial Fever Produced by Physical Means: Its Development and Application. By CLARENCE A. NEYMANN, A.B., M.D., F.R.S.M. 294 pages. Charles C. Thomas, Springfield and Baltimore. 1937. Price, $6.00.

The book is well planned, nicely illustrated and very well printed, though the print is rather small. It is divided into 15 chapters including The Basic Theories and Principles, History, Physiology (two chapters), Technic of Electropyrexia, Dementia Paralytica, Syphilis of the Central Nervous System, Primary and Secondary Syphilis, Multiple Sclerosis, Chorea Minor, Arthritis, Gonorrhoea, Asthma, Other Diseases, Dreams and Facts. There is a preface, a subject and an author index and an extensive bibliography of 556 references.

The author's chief interests are in psychiatry and his material was drawn mainly from that field. He was the first to produce artificial fever for therapeutic purposes by means of diathermy, a fact that the reader is never for a moment allowed to forget. This insistence somewhat mars the book; nevertheless, it is a valuable exposition of a method of therapy that is now exciting widespread interest.

T. P. S.

Digestive Tract Pain, Diagnosis and Treatment, Experimental Observations. By CHESTER M. JONES. The Macmillan Co., New York, 1938. 152 pages. Price, $2.50.

Over a period of fourteen years the writer has been interested in the subject of pain arising from the viscera of the digestive canal. Long series of normal individuals and of patients have been studied as to the nature and site of their painful sensations when a small balloon was inflated, causing distention at a definite level in the tract. In general, the results are confirmatory of those obtained by others. The presentation of these experiments yields an interesting review of the subject. The practical deductions which may be drawn from such knowledge are indicated in the latter half of the book which is given up to case protocols. It is a book which will stimulate a more thoughtful consideration of the diagnostic value of pain.

M. C. P.

The Culture of Organs. By ALEXIS CARREL and CHARLES A. LINDBERGH. Paul B. Hoeber, Inc., New York. 1938. 221 pages. Price, $4.50.

The culture of organs in vitro could not be successfully achieved until many difficulties had been overcome. A medium must be perfused through an organ under a pulsatile pressure. This medium, as well as the organ, must remain sterile. The fluid must be kept suitably oxygenated, free of particles and exactly adjusted as to temperature, osmotic pressure, pH and maximum and minimum pressures. In 1931 Lindbergh devised an apparatus which could be kept sterile but it failed in other particulars. It was only in 1934 that the first form of the successful pump was obtained and the following year when the organ chamber was perfected. Successful perfusion of living organs for periods of weeks ensued. Since 1935 numerous experiments have been carried out with this technic by the senior author and others, exploring the effects upon the structure and function of living organs of induced variations in their milieu. It is obvious that by this means a series of hitherto inaccessible problems may be attacked.

The description of the philosophy of the method is in interesting contrast to the clear and precise instructions for the construction and operation of the apparatus. The conjunction of separate abilities was needed to make available this valuable new tool for biological research.

M. C. P.

Tuberculosis Among Children and Young Adults. By J. ARTHUR MYERS. 2nd Edition. 401 pages. Chas. C. Thomas, Springfield, Ill., and Baltimore, Md. 1938. Price, $4.50.

The author has devoted the greater part of this book to a description of the nature of the first infection type and of the reinfection type of tuberculosis in infants, children and young adults, and particularly to discussion of how these young individuals acquire these lesions and how they may spread them. He tries hard to impart to the reader his own zeal for stamping out tuberculosis. Since he has had an unusually full experience in tuberculosis detection and in the working out of preventive measures his book is very interesting and valuable from these points of view. It is, however, touched with the optimism of the crusader. The author seems a bit uncritical and shows little desire to weigh and evaluate contrary opinions.

There is a lack of clinical description of the disease. Indeed our interest in the clinical aspects is rather rebuffed and we are led firmly back to periodic tuberculin tests and routine roentgen-rays of positive reactors.

On the whole this is a valuable book on the pathogenesis and on the prevention of tuberculosis in the earlier years of life but the practising physician will need another volume on the clinical details to attain a balanced view of the subject.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College Library

The following gifts to the College Library are gratefully acknowledged:

Rear Admiral Charles S. Butler, F.A.C.P., M.C., U. S. Navy—1 reprint;
Dr. Julius P. Dworetzky, F.A.C.P., Liberty, N. Y.—2 reprints;
Dr. Herbert R. Edwards (Associate), New York, N. Y.—3 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—Third, Second Series, Supplement to "Gutman's Modern Drug Encyclopedia";
Dr. Lynn T. Hall, F.A.C.P., Omaha, Nebr.—1 reprint;
Dr. Irving R. Juster (Associate), Glens Falls, N. Y.—3 reprints;
Dr. Albert Benjamin McCreary (Associate), Jacksonville, Fla.—1 reprint;
Dr. Morris E. Missal, F.A.C.P., Rochester, N. Y.—2 reprints;
Dr. William Nimeh, F.A.C.P., Mexico City, Mexico—2 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint;
Dr. Kenneth Phillips, F.A.C.P., Miami, Fla.—2 reprints;
Dr. Edwin T. Thorsness, F.A.C.P., Denver, Colo.—5 reprints;
Dr. Emil G. Vrtiak (Associate), Chicago, Ill.—2 reprints.

New Life Member

Dr. George Bruce Lemmon, F.A.C.P., Springfield, Mo., has lately become a Life Member of the American College of Physicians.

American Board of Internal Medicine

Written examinations for certification by the American Board of Internal Medicine will be held in various parts of the United States on Monday, October 17, 1938, and on Monday, February 20, 1939.

Formal application must be received by the Secretary before September 15, 1938, for the October, 1938, examination, and on or before January 1, 1939, for the February, 1939, examination.

Application forms may be obtained from William S. Middleton, M.D., Secretary-Treasurer, 1301 University Ave., Madison, Wis.

At the annual meeting of the Santa Clara County Tuberculosis Association held at San Jose, Calif., in June, 1938, the guest speaker was Dr. Francis M. Pottenger, Sr., F.A.C.P., Monrovia, Calif.

Dr. C. Kelly Canelo, F.A.C.P., San Jose, Calif., was elected President of the Santa Clara County Tuberculosis Association for the coming year.

The Committee of Physicians held its first annual meeting at Cornell University Medical College, New York City, July 21. Dr. Richard M. Smith of Harvard Medical School was elected chairman. Dr. Hugh Cabot, Rochester, Minn., and Dr. William J. Kerr, F.A.C.P., San Francisco, were elected vice chairmen. Dr. Russell L. Cecil, F.A.C.P., New York, the retiring chairman, was elected honorary chairman,

and Dr. John P. Peters, New Haven, was reëlected secretary. The deliberations of the Committee were closed to the press.

Dr. Carleton B. Peirce, F.A.C.P., for a number of years Associate Professor of Roentgenology at the University of Michigan Medical School and the University Hospital, Ann Arbor, has received the appointment as Director of the Department of Radiology at the Royal Victoria Hospital, Montreal, succeeding Dr. A. Howard Pirie.

At the invitation of the Vitamin Advisory Board of the U. S. Pharmacopoeia, a notable gathering of vitamin experts, some ninety in number, took place in New York on July 22 and 23. The discussion covered tests and bio-assays for new vitamin preparations to be introduced into the Pharmacopoeia. Among other things, it was recommended that solutions of three strengths of vitamins A and D be prepared in corn or cottonseed oil to eliminate the fishy taste and odor of cod liver oil, and that a preparation of vitamin A be furnished without D. As President of the U. S. Pharmacopoeia Convention, Dr. Walter A. Bastedo, F.A.C.P., New York, took part in the deliberations.

Dr. Anita M. Mühl, F.A.C.P., San Diego, Calif., has accepted a call for three years to lecture at the University of Melbourne, Australia.

Dr. William J. Mallory, F.A.C.P., President of the Medical Society of the District of Columbia, and Dr. Frederick A. Willius, F.A.C.P., of the Mayo Clinic, Rochester, Minn., will be guest speakers on the program of the Sixty-ninth Annual Session of the Medical Society of Virginia at Danville, October 4, 5 and 6, their respective subjects being, "The Diagnostic Value of the Clinical Aspects of Digestive Disease" and "The Effects of Protracted and Recurrent Congestive Heart Failure on the Liver."

Round Table conferences will be a feature of this Society's meeting this year, and the following members of the College are among leaders:

Dr. Walter B. Martin, F.A.C.P., Norfolk, and Dr. David P. Scott, F.A.C.P., Lynchburg—Acute Respiratory Diseases;
Dr. Oscar Swineford (Associate), University—Allergic Diseases;
Dr. A. B. Hodges, F.A.C.P., Norfolk, and Dr. F. H. Smith, F.A.C.P., Abingdon—Etiology and Treatment of Indigestion;
Dr. George B. Lawson, F.A.C.P., Roanoke—The Vitamins.

Dr. B. R. Kirklin, F.A.C.P., Head of the Section on Roentgenology at the Mayo Clinic and Professor and Director of the Division of Radiology, Mayo Foundation, will act as the leader of a Round Table conference on Radiology before the annual meeting of the Virginia Radiological Society in October. Dr. Kirklin is a past president of the American Roentgen Ray Society and at present chairman of the Section on Radiology of the American Medical Association.

The American Medical Association will meet in St. Louis in 1939, New York in 1940 and Cleveland in 1941. Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., Governor of the College for Wisconsin, is now President-Elect.

Dr. Beverley R. Tucker, F.A.C.P., Richmond, Va., gave a series of six lectures in neuropsychiatry before the Florida State Medical Association at Daytona Beach during June.

With Surgeon General Thomas Parran, F.A.C.P., acting as chairman, a meeting of laboratory workers from the entire country and physicians and health officers interested in the control of syphilis will be held in Hot Springs, Ark., October 21 to 22, under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis of the United States Public Health Service.

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., has been elected President, and Dr. J. Burton Glenn, F.A.C.P., Washington, D. C., has been elected Treasurer of the George Washington University Medical Society.

Dr. Earl B. McKinley, F.A.C.P., Washington, was elected President of the American Association of Pathologists and Bacteriologists at its last meeting. At the time this news note is prepared, we note with grave concern that Dr. McKinley was a passenger on the Hawaii Clipper, which apparently has been lost in the Pacific on July 28.

Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon General of the U. S. Public Health Service, Washington, has been made Medical Officer in Charge of the Federal Narcotic Farm at Lexington, Ky., succeeding Dr. Lawrence Kolb, F.A.C.P., who has been transferred to Washington to become Assistant Surgeon General.

Dr. C. R. Bennett, F.A.C.P., Eufaula, Ala., and Dr. Seale Harris, F.A.C.P., Birmingham, Ala., have been elected Second Vice President and Member of the Council, respectively, of the Chattahoochee Valley Medical Association.

Dr. Edgar Hull, F.A.C.P., has been elected Vice President of the Faculty Club of Louisiana State University School of Medicine, New Orleans.

Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, has been elected a Vice President of the Medical and Chirurgical Faculty of Maryland.

Dr. Leon S. Lippincott, F.A.C.P., Vicksburg, Miss., is Secretary of the Hospital Service Corporation of Mississippi.

Dr. Frank D. Gorham, F.A.C.P., and Dr. L. P. Gay, F.A.C.P., both of St. Louis, have been elected President and Treasurer, respectively, of the Missouri Chapter for the Advancement of Gastroenterology.

Dr. D. W. Carter, F.A.C.P., Dallas, Dr. W. W. Bondurant (Associate), San Antonio, and Dr. V. E. Schulze, F.A.C.P., San Angelo, have been elected President, Vice President and Secretary, respectively, of the Texas Railway Surgeons Association.

Dr. William B. Newcomb, F.A.C.P., Norfolk, has been elected President of the Norfolk County (Va.) Medical Society.

Dr. Myrtelle M. Canavan, F.A.C.P., Curator of the Warren Anatomical Museum at Harvard, is a member of the editorial board of the American Medico-Legal Association, with headquarters in Boston. Dr. Frederick C. Warnshuis of San Francisco, formerly secretary of the California Medical Association, has accepted the presidency and editorship-in-chief of this organization.

Dr. Julius H. Hess, F.A.C.P., and Dr. Robert A. Black, F.A.C.P., both of Chicago, were among the lecturers in a graduate course in obstetrics and pediatrics conducted at Research and Educational Hospital, Chicago, during July and August. The course was given under the auspices of the University of Illinois.

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., Dr. William D. Sansum, F.A.C.P., Santa Barbara, Calif., and Dr. Lawrence Reynolds, F.A.C.P., Detroit, Mich., will be guest speakers on the program of the Sixteenth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, October 3 to 6.

Dr. Edgar A. Hines, F.A.C.P., Seneca, S. C., was honored at a recent meeting of the South Carolina Medical Association, at which a silver tray, pitcher and goblets were presented to him in recognition of his long service as Secretary and Editor of the journal of that Association. Dr. Hines has been Secretary since 1909 and Editor of the Journal since 1912.

Dr. Henry Chesley Bush, F.A.C.P., Livermore, Calif., has been elected President of the National Tuberculosis Association; Dr. Frederick T. Lord, F.A.C.P., Boston, and Dr. Paul P. McCain, F.A.C.P., Sanatorium, N. C., were elected vice presidents.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, has been elected President of the International Congress on Rheumatism. The next meeting of this body will be held in New York during June, 1940.

Dr. Cecil O. Lorio, F.A.C.P., Baton Rouge, La., gave a refresher course on pediatrics in Marksville, La., June 13 to 17, under the auspices of the committees on medical education and pediatric courses of the State Medical Society and the Bureau of Parish Health Administration and the Division of Maternal and Child Health of the State Board of Health.

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn., is President of the American Society of Clinical Pathologists.

In recognition of his many years of service, Dr. William H. Marshall, F.A.C.P., Flint, Mich., has been made Director Emeritus of the Department of Internal Medicine at Hurley Hospital.

Dr. Benjamin B. Souster, F.A.C.P., St. Paul, has been elected Secretary of the Minnesota State Medical Association.

Dr. O. H. Perry Pepper, F.A.C.P., Professor of Medicine in the University of Pennsylvania School of Medicine, was the recipient of the honorary degree of Doctor of Science from Lafayette College, Easton, Pa., at its recent commencement.

Dr. Thomas D. Cunningham, F.A.C.P., Denver, Colo., and Dr. Joseph C. Kamp, F.A.C.P., Casper, Wyo., addressed the thirty-fifth annual meeting of the Wyoming State Medical Society at Laramie, during August, on "The Treatment of Severe Asthmatics" and "Use and Abuse of Sulfanilamide," respectively.

Dr. David P. Barr, F.A.C.P., St. Louis, is President of the Association for the Study of Internal Secretions. The next meeting of this Association will be held in St. Louis during the spring of 1939.

Dr. Oliver P. Kimball, F.A.C.P., Cleveland, Dr. James B. Collip, F.A.C.P., Montreal, Dr. Henry J. John, F.A.C.P., Cleveland, and Dr. David Marine, F.A.C.P., New York City, were speakers on the program of the International Goiter Conference held in Washington, D. C., September 12 to 14. The American Association for the Study of Goiter and the Medical Society of the District of Columbia acted as hosts.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, was one of the speakers at the dedication of the Hall of Science of the Golden Gate International Exposition at San Francisco during June.

Dr. Charles P. Cake (Associate) has been appointed Chief Medical Officer in Tuberculosis at the Gallinger Hospital, Washington, D. C.

OBITUARY

DR. EARL BALDWIN McKINLEY

Dr. Earl Baldwin McKinley (F.A.C.P. 1924), Dean of the Medical School, Professor of Bacteriology and Director of Medical Research, George Washington University was one of the fifteen persons aboard the 26-ton Hawaii Clipper which disappeared on July 28, 1938, under most mysterious circumstances en route from Guam to Manila. A thorough systematic search in which all branches of the military forces of the United States stationed in the Philippines took part, assisted by the Commonwealth of the Philippines and Japan, failed to disclose a single vestige of the superliner or its occupants other than a mixture of gasoline and oil on the surface of the water near the zone from which radio communication was last received. There seems to be no doubt but that the transport plunged into the Pacific Ocean at one of its deepest points under conditions the nature of which will probably never be revealed.

Earl McKinley was born at Emporia, Kansas, on September 28, 1894. He prepared for college at the Newton High School, Newton, Kansas, and entered the University of Michigan on the combined curriculum in letters and medicine September 27, 1912. He received the degree of A.B. in 1916. His work in the medical school was interrupted by the world war. He entered the service May 7, 1917, going directly to the Reserve Officers Training Camp at Fort Sheridan, Illinois, and was discharged August 8, 1919, with the rank of first lieutenant. He was with the Rainbow Division overseas and saw action in the Marne offensive of July and August 1918. In September, 1919, he returned to the University to complete the medical course and in 1922 was granted the degree of M.D. During this period he served as an assistant in bacteriology and was an instructor in physiological chemistry. In these capacities he came into direct contact with Dr. F. G. Novy, whose stimulating influence he frequently acknowledged and whose advice and aid he constantly sought.

Shortly after completing the required program of study in medicine and before entering on an internship for which he had qualified, Dr. McKinley was appointed assistant professor of bacteriology and pathology at Baylor University, Dallas, Texas. While at Baylor he investigated some of the fundamental aspects of the d'Herelle phenomenon and the clinical application of the bacteriophage in the treatment of a number of disorders, especially bacillary dysentery. These experiences crystallized his thoughts and he realized his interests were in research rather than the practice of medicine. Therefore, in the spring of 1924, although he had been advanced to a full professorship and head of the department of bacteriology, he applied for and was granted a National Research Council Fellowship in the medical sciences. He arrived with his family in Brussels in August, 1924, and at once went to work under Professor Jules Bordet at the Pasteur In-

stitute. This contact with foreign workers which extended over a year was of inestimable value and resulted in the publication of four papers on certain aspects of immunity.

While in residence abroad he accepted an appointment as assistant professor of bacteriology in the College of Physicians and Surgeons of Columbia University and arrived in New York in the fall of 1925 to assume his duties. For two years he shouldered his full share of the regular instructing load and developed a special course in the filterable viruses. His renewed interest in the ultraviruses was the natural outgrowth of his early experiences with the bacteriophage and now broadened to encompass such diseases as poliomyelitis and encephalitis lethargica. His services were promptly recognized by an advancement in rank to that of associate professor of bacteriology. An inherent faculty for organizing and administration led to his selection in the establishment of the division of bacteriology at the new School of Tropical Medicine in Puerto Rico and he spent several weeks in this capacity in Puerto Rico in September 1926. It was during this activity that he became imbued with the necessity for a greater breadth of experience. Accordingly, he relinquished his connections in New York and arrived in Manila early in June, 1927 to take the position as field director with the International Health Division of the Rockefeller Foundation. He was charged with the duty of reorganizing the public health laboratory service in the Bureau of Science coöperating with the Department of Health of the insular government. This undertaking was satisfactorily consummated within the year. In the meantime, a new School of Hygiene and Sanitation was established in affiliation with the medical school of the University of the Philippines, and McKinley taught bacteriology there for one trimester. The demands of either of these assignments were enough to keep an ordinary individual occupied, but he found time to assemble the data for and to write a monograph of 412 papers on "Filterable Viruses and Rickettsia Diseases."

Having accomplished the task for which he was originally sent to the Philippines and fearing that the projected plans of the Foundation would involve him in endless administrative detail and thus submerge experimental work, he was quite willing to rejoin his old department at Columbia when the call came in the spring of '28. He was appointed professor of bacteriology and director of the School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University. Again he moved his family half way around the world and in September 1928 took up his duties in San Juan shortly after the island had experienced one of its most devastating storms. For three years he devoted himself unsparingly to the development of the School of Tropical Medicine and the Hospital and their relationship to the local medical problems and medical profession. His sponsoring of the establishment of the *Puerto Rico Journal of Public Health and Tropical Medicine* on a quarterly basis which has

served as the principal medium for publications from the school was an outstanding achievement. This journal has appeared regularly and has gained an enviable reputation in its particular field. Administrative duties in this new assignment were very demanding but odd moments were found for the bacteriological investigation of a number of local diseases.

The summer of 1930 was spent in residence at the University of Chicago, where, in the capacity of a visiting professor, he presented a special course on the ultraviruses. At this time he realized that his two children born while he was still a medical student in Ann Arbor were rapidly approaching the age where the demands of their education could be satisfied only in the States. Accordingly, they were placed in school here, and he and Mrs. McKinley returned to San Juan in the fall. This break in the home life he appreciated was only the beginning of a long period away from the children and he concluded that under these circumstances his connections in Puerto Rico could not be permanent. In the winter of 1931 in collaboration with the writer, studies on leprosy were begun at the School of Tropical Medicine. Attempts were made to cultivate the causative agent of this disease and to transmit the malady to laboratory animals. The results of these experiments were published, and in 1937 McKinley spent his sabbatical leave in the Philippines confirming and extending these investigations. He had with him on the flying boat a number of specially prepared substances which were to be used in the skin-testing of patients with leprosy in Manila.

In September 1931, he accepted the Deanship of the Medical School of George Washington University and took up his abode in Washington. In this new environment the prodigious energy of the man was unleashed. It would be impossible to enumerate the ramification of his activities or his accomplishments over the past seven years. He threw himself unstintingly into the task of reorganizing the staff and physical plant of the medical school. Under his direction this proceeded with a minimum of delay and conflict, and the present condition of the institution is a monument to his efforts. He was a born leader, and in Washington the multiplicity of scientific organizations with which he promptly affiliated responded to the stimulus of his personality. His proved ability as an administrator was responsible for his appointment to innumerable committees and election to executive positions in a large number of organizations. At the time of his disappearance, to mention only a few of his affiliations, he was president of the Society of Pathologists and Bacteriologists; executive secretary of the American Foundation of Tropical Medicine which with the Academy of Tropical Medicine owes its existence to his indefatigable interest in tropical diseases; and a member of the executive committee of the American Association for the Advancement of Science. The services of Dr. McKinley in this latter organization, first as Secretary of Section N (medical) and then as a member of the executive committee were outstanding and are worthy of special acclaim. He gave freely of his time in the preparation of the

programs of the medical section and his contributions to the deliberations of the executive committee were significant and far reaching.

One might conclude that the demands of the aforementioned interests would preclude active participation in research, but such was not the case. He continued his investigations of the ultraviruses and published a number of papers in this field, as well as on leprosy. In addition, under the sponsorship of the National Research Council he conducted a survey of tropical medicine, spending considerable time abroad in the gathering of the data. This material was published in a monograph entitled "A Geography of Disease" and is recognized as a valuable contribution. On the tragic voyage he was extending this study by taking samples of the microbic content of the air at various points over the Pacific which were to be later identified in an effort to unravel the enigma of the trans-oceanic spread of pathogenic organisms.

In 1917, he married a classmate, Leola Edna Royce of Saulte Ste. Marie, Michigan, who survives him. Two children were born to them; Janet and Royce, both of whom are in college. Mrs. McKinley, although never robust, was ever his constant companion and usually accompanied him on all of his trips. Their hospitable home was open to a host of loving friends. His untimely death at the height of a brilliant career has removed prematurely one who had given his full share, but who had still much to give. His loyalty, friendship and generous support of all worthy enterprises have enriched the world.

MALCOLM H. SOULE.
Ann Arbor, Mich.